Quantifying the Clinical and Cost-Effectiveness of Primary Endocrine Therapy Compared with Surgery for Oestrogen Receptor Positive Breast Cancer in Older Women

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Contents

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List of abbreviations

95%CI	95% confidence interval
ACM	All-cause mortality
AI	Aromatase inhibitor
AIC	Akaike Information Criteria
ALND	Axillary lymph node dissection
BCS	Breast conservative surgery
BCSM	Breast cancer-specific mortality
BIC	Bayesian Information Criteria
BNF	British National Formulary
BT	Biological treatment
CBA	Cost-benefit analysis
CCI	Charlson Comorbidity Index
CE plane	Cost-effectiveness planes
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CGA	Comprehensive geriatric assessment
CHD	Coronary heart disease
CHEERS	the Consolidated Health Economic Evaluation Reporting Standards
Cox PH	Cox's proportional hazard regression
CPRD	Clinical Practice Research Datalink
CQC	Care Quality Commission
CR	Cancer Registry database
CT	Chemotherapy
CUA	Cost-utility analysis
DCIS	Ductal carcinoma in situ
DOB	Date of birth
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D	EuroQol-5 dimensions
ER	Oestrogen receptors
ET	Endocrine therapy
EUSOMA	European Society of Breast Cancer Specialists
EVPI	Expected Value of Perfect Information
EVPIM	Expected Value of Perfect Implementation
GP	General practitioner
HER2	Human epidermal growth factor receptor 2

HES	Hospital Episode Statistics
HFRS	Hospital Frailty Risk Score
HGR	Healthcare Resource Group
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health State Utility Value
ICC	Intra-class correlation coefficients
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
IMD	Index of Multiple Deprivation
INMB	Incremental net monetary benefit
IPTW	Inverse probability treatment weight
IQR	Interquartile range
ISAC	Independent Scientific Advisory Committee
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KM	Kaplan-Meier analysis (or survival)
NABCOP	National Audit of Breast Cancer in Older Patients
NB	Net benefits
NCRAS	National Cancer Registration and Analysis Service
NHS	National Health Service
NICE	The National Institute of Health and Care Excellence
NMB	Net Monetary Benefit
NPI	Nottingham prognostic index
OECD	Organisation for Economic Cooperation and Development
ONS	the Office for National Statistics Mortality Data
OPCS	Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures
OS	Overall survival
PartSA	partitioned survival analysis
PET	Primary endocrine therapy
PFS	Progression-free survival
PR	Progesterone receptors
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Systematic Reviews
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
QoL	Quality of life

RCT	Randomised control trial
RR	Relative risk
RT	Radiotherapy
SD	Standard deviation
SE	Standard error
SEER	the Surveillance, Epidemiology, and End Results
SF-6D	Short-Form Six-Dimension
SG	Standard gamble
SIOG	International Society of Geriatric Oncology
SLNB	Sentinel lymph node biopsy
SMD	Standardised mean difference
TNM	tumour node metastasis cancer-staging scheme
TTF	Time to treatment failure
TTO	Time trade-off
UK	the United Kingdom
US	the United States
VOI	Value of Information
WHO	World Health Organisation

Terms of glossary

Breast-conserving surgery

Breast-conserving surgery (lumpectomy) removes the tumour and lymph nodes, leaving as much healthy breast tissue as possible.

Care pathway

A pathway that describes the sequence of health technologies delivered to a patient over time in routine clinical practice.

Cluster-robust standard errors

They are used when data are clustered (for example, patients within different hospitals) to account for the potential within-cluster correlation between observations.

Cohort study

A cohort study is a longitudinal study in which researchers monitor and observe a chosen population over an extended period.

Conceptual model

An abstract representation of a phenomenon of interest, often illustrated diagrammatically, to assist in determining the final structure of a de novo decision analytic model.

Cost-effectiveness acceptability curve

A graphical illustration of the probability that each alternative comparator strategy is relatively cost-effective (Y-axis) over a range of cost-effectiveness thresholds (X-axis).

Cost-effectiveness threshold

The additional cost must be imposed on the budget for health care to displace one QALY elsewhere within the health care system.

Cox proportional hazard regression

The Cox proportional-hazards regression is a model commonly used statistically in medical research to investigate the association between the survival time of patients and one or more predictor variables.

Decision analytic model

A series of mathematical relationships that represent the progression of a patient's disease and the impact of health technology on disease progression. The output of a decision analytic model can be expressed in terms of the expected outcomes of interest for each alternative comparator strategy.

Decision problem

It is an explicit statement of the resource allocation decision under consideration.

Decision uncertainty

The probability that an incorrect decision is made in the context of resource allocation decisions for health care.

Deterministic sensitivity analysis

To establish the sensitivity of the expected outcomes derived from an economic evaluation by manually adjusting the value(s) of a model's input parameter(s).

Dominance

Health technology is dominated if a comparator strategy produces more health at a lower cost.

Economic evaluation

"…the comparative analysis of alternative courses of action in terms of both their costs and consequences". An alternative typically refers to a health technology; the consequence is typically expressed in terms of health benefits.

Endocrine therapy

Endocrine therapy (hormone therapy or hormone treatment) slows or stops the growth of hormone-sensitive tumours by blocking the body's ability to produce hormones or interfering with the effects of hormones on breast cancer cells.

Extended dominance

Health technology is extendedly dominated if a linear combination of two alternatives produces more health at a lower cost.

Health technology

An intervention used in the delivery of health care. For example, a pharmaceutical treatment, medical test, or device.

Incidence

The rate of new cases within a specific population over a period.

Incremental cost

The difference in cost between the two alternative interventions.

Incremental cost-effectiveness ratio

The ratio of incremental costs to incremental health benefits.

Incremental QALY

The difference in QALYs between the two alternative interventions.

Inverse probability of treatment weight

Inverse probability of treatment weight is a statistical technique for calculating statistics standardized to a pseudo-population different from that in which the data was collected to predict the likelihood of receiving two treatments.

Kaplan Meier survival analysis

The Kaplan–Meier estimator is a non-parametric statistic used to estimate the survival function from lifetime data and to calculate survival time after treatment.

Mastectomy

A mastectomy is a type of surgery that removes the entire breast.

Monte Carlo simulation

The process of random sampling.

National Institute for Health and Care Excellence

The decision-making authority is responsible for making recommendations regarding allocating population healthcare resources in England.

Opportunity cost

The benefit forgone from the next-best use of a specific resource. The opportunity cost of resource allocation decisions for health care can be expressed in the health benefits forgone.

Perspective

The scope of the costs that should be included in an economic evaluation. The budget constraint of the decision-maker typically defines the perspective. Examples include a health care system perspective and a societal perspective.

Prevalence

The proportion of cases within a specific population at a specific period.

Probabilistic sensitivity analysis

To propagate joint parameter uncertainty through an analytic decision model by (i) characterising all input parameters as probability distributions and (ii) sampling values for all parameters using Monte Carlo simulation.

Propensity score technique

The propensity score is a statistical technique that attempts to estimate the effect of a treatment, policy, or other intervention by accounting for the covariates that predict receiving the treatment. It attempts to reduce the bias due to confounding variables found in an estimate of the treatment effect obtained from comparing outcomes among units that received the treatment versus those that did not.

Quality-adjusted life year

A generic outcome measure of health benefit is calculated by multiplying each year of life by a weight representing the health-related quality of life. Weights are calculated according to the reference points of one (full health) and zero (death); states worse than death are possible.

Randomised control trial

Randomised control trial (RCT) is an experimental study designed to evaluate the clinical efficacy or effectiveness compared with a placebo or standard treatment.

Reference case

It is a pre-specified preferred criterion for conducting an economic evaluation. A reference case is an expression of a decision-makers value judgements.

TNM staging system

The TMN cancer-staging scheme comprises three elements: the tumour size (T), lymph nodes state (N) and metastatic states (M). Breast cancer can be categorised into four stages depending on the status of three elements: Stages I, II, III and IV.

Value of information

A set of methods derived from statistical decision theory that quantifies the potential value of producing further prospective research to reduce the parameter (and decision) uncertainty associated with making decisions based on expected outcomes.

Value of implementation analysis

A value of implementation analysis quantifies the value of improving the uptake of surgery in this population of patients.

Abstract

The increasing number of women diagnosed with breast cancer at an older age (⩾ 70 years) led to challenges in optimising treatment strategies for this population. Surgery is the recommended first-line treatment for women with early-stage breast cancer in England. In contrast, primary endocrine therapy (PET) is suggested for patients with oestrogen receptor-positive and shorter life expectancy who are unfit for surgery due to frailty or co-morbidity. However, PET has been widely used as an alternative to surgery for older women with oestrogen receptor-positive (ER+) early-stage breast cancer.

The synthesised data of seven randomised controlled trials indicated no statistical difference in overall survival between surgery and PET for treating older patients who are physically fit for surgery. However, limited comparative effectiveness data compares these two treatments in the real world. Besides, there is a lack of economic evidence to inform the cost-effectiveness of PET versus surgery in older women with early-stage breast cancer.

This thesis aimed to generate economic evidence of PET versus surgery in older women with oestrogen receptor-positive early-stage breast cancer to inform the healthcare decision-making by clinicians, patients and policymakers. Five individual studies were conducted sequentially to fulfil the thesis aim, including: (1) two systematic reviews to appraise current evidence sources estimating input parameters used in model-based economic evaluations in postmenopausal women with primary breast cancer and (2) to estimate health state utility values of women with breast cancer and their correlation with age; (3) a lifetime Markov model with six month cycle length based on randomised control trials comparing the cost-effectiveness and value of implementation of PET versus surgery in older patients who were 'physically fit for surgery' from the perspective of National Health Service (NHS) England and Personal Social Services using the 2020/21 prices; (4) a cohort study using a large longitudinal datalink in England to investigate the

impact of frailty and comorbidity on the comparative clinical effectiveness of PET versus surgery; (5) a same model-based economic evaluation of PET versus surgery for older women with early-stage breast cancer who are 'frail and potentially 'unfit for surgery'.

In line with the national recommendation for operable women with breast cancer, surgery is still a cost-effective use of health care resources for older patients who are fit for surgery or have minor physical issues (i.e., pre-frail) based on current evidence. The results indicated that PET had a higher cost (£27,459.51) and more QALYs gained (0.16), translating them into the ICER was £173,395.82 per QALY gain. The cohort study demonstrated that the hazard ratios of breast cancer-specific mortality comparing PET with surgery reduced from 3.0 (95%CI: 2.8, 3.2) in older patients at the non-frail level to 1.2 (95%CI: 0.9, 1.8) at the frail level; and from 3.0 (95%CI: 2.8, 3.3) at the low CCI level to 1.5 (95%CI: 1.1, 2.1) at the high CCI level. Based on the findings of the cohort study, a further economic evaluation was indicated for the patients who are at high levels of HFRS. PET is a cost-effective strategy with an incremental cost and QALYs of £7,351.48 and 0.38, translating into the ICER of £19,498.08 per QALY gain.

The value of information analysis indicated it was valuable to conduct further research. Specifically, further evidence on the clinical effectiveness of interventions for older patients who are physically unfit for surgery (i.e., patients with frailty or multiple comorbidities) is required. This thesis highlighted that PET is a potentially cost-effective strategy for frail older patients in the UK, and surgery is still a first-line strategy for older patients who are physically fit for surgery or have mild-moderate frailty.

Declaration

No portion of the work referred to in the thesis has been submitted to support an application for another degree or qualification from this or any other university or institute of learning.

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List of publications

The dissemination of the research in this thesis, to date, is described below in terms of peer-reviewed publications and conference proceedings. A complete publication strategy to disseminate the research further is reported in Appendix 1.

Peer-reviewed publications

Chapter 3

Yubo Wang, Sean P. Gavan, Douglas Steinke, Kwok-Leung Cheung, Li-Chia Chen. Systematic review of the evidence sources applied to cost-effectiveness analyses for older women with primary breast cancer. *Cost Effectiveness and Resource Allocation*, 2022; 20(9). https://doi.org/10.1186/s12962-022-00342-7 (Appendix 3)

Chapter 4

Yubo Wang, Sean P. Gavan, Douglas Steinke, Kwok-Leung Cheung, Li-Chia Chen. The impact of age on health utility values for older women with early-stage breast cancer: a systematic review and meta-regression. Health and Quality of Life Outcomes. 2022;20(1):169. https://doi.org/10.1186/s12955-022-02067-w (Appendix 8)

International conference publications

Chapter 3

Yubo Wang, Sean Gavan, Douglas Steinke, Li-Chia Chen. Appraising current evidence to inform the cost-effectiveness of primary endocrine therapy for treating older women with primary breast cancer. *Prescribing and Research in Medicines Management (PRIMM) (UK & Ireland) conference*. 17 January 2020, Manchester, United Kingdom. *Pharmacoepidemiology and Drug Safety* 2020; 29:9-10. https:///doi.org/10.1002/pds.5518 (Poster presentation).

Yubo Wang, Sean Gavan, Douglas Steinke, Li-Chia Chen. A systematic review of cost-effectiveness evidence to support primary endocrine therapy for treating older women with primary breast cancer. *European Drug Utilisation Research Group Conference (EuroDURG)*. 4-7 March 2020. Szeged, Hungary. (Poster presentation).

Chapter 5

Yubo Wang, Sean P. Gavan, Douglas Steinke, Kwok-Leung Cheung, Li-Chia Chen. Health and economic loss of primary endocrine therapy to older women with operable

early-stage breast cancer - A cost-effectiveness and value of implementation analysis. *Prescribing and Research in Medicines Management (PRIMM) (UK & Ireland) conference.* 10 June 2022, Manchester, United Kingdom. *Pharmacoepidemiology and Drug Safety* 2022; 31:1. https://doi.org/10.1002/pds.5499. (Poster presentation, the best poster award).

Chapter 6

Yubo Wang, Sean Gavan, Douglas Steinke, Li-Chia Chen. An evaluation of survival of women treated with surgery vs primary endocrine therapy for breast cancer and healthy women. The 38th *International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE)*, Copenhagen, Denmark, 26–28 August 2022. *Pharmacoepidemiology and Drug Safety* 2022; 31:503. https://31: 3-628. /doi.org/10.1002/pds.5518. (Poster presentation).

Yubo Wang, Sean Gavan, Douglas Steinke, Li-Chia Chen. Evaluation of survival of women with early breast cancer receiving surgery vs primary endocrine therapy. The 38th *International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE)*, Copenhagen, Denmark, 26–28 August 2022. *Pharmacoepidemiology and Drug Safety* 2022; 31:314-315 https://31: 3-628. /doi.org/10.1002/pds.5518. (Poster presentation).

Yubo Wang, Sean Gavan, Douglas Steinke, Li-Chia Chen. Frailty-gradient risk of mortality comparing primary endocrine therapy and surgery in treating women with early breast cancer. The 38th *International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE)*, Copenhagen, Denmark, 26–28 August 2022. *Pharmacoepidemiology and Drug Safety* 2022; 31:14-15. https://31: 3-628. /doi.org/10.1002/pds.5518. (Podium presentation).

Chapter 7

Yubo Wang, Sean P Gavan, Douglas Steinke, Kwok-Leung Cheung, Li-Chia Chen. A cost-effectiveness and value of information analysis comparing surgery versus primary endocrine therapy for frail older women with early-stage breast cancer. *Prescribing and Research in Medicines Management (PRIMM) (UK & Ireland) conference*. 10 June 2022, Manchester, United Kingdom. *Pharmacoepidemiology and Drug Safety* 2022; 31:15-16. https://doi.org/10.1002/pds.5499. (Poster presentation).

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Chapter 1 Introduction

As the preface, Chapter 1 highlights the background of this PhD research motivation (Section 1.1), overviews the aim and objectives of the PhD project (Section 1.2) and outlines the navigating structure of this thesis (Section 1.3).

1.1 Background

Breast cancer survival has dramatically improved in England by implementing screening programmes and innovative treatment [1, 2]. According to the clinical guidelines by the National Institute for Health and Care Excellence (NICE) in England [3], surgery is recommended as the first-line treatment with superior clinical effectiveness for women with early-stage breast cancer (means operable breast cancer), irrespective of chronological age at diagnosis. In England, postmenopausal women (defined as women aged ≥ 50 years) are the high-risk group for breast cancer diagnosis, and 80% of patients with breast cancer are diagnosed at the early stage [4, 5].

However, an increasing proportion of postmenopausal patients have been diagnosed at an older age in recent decades due to the ageing population. Older patients, i.e., postmenopausal women with early-stage breast cancer at an older age (aged ≥ 70 years), may not receive surgery as their initial treatment strategy. Instead, primary endocrine therapy (hereafter referred to as 'PET' in this thesis) has been widely used as an alternative strategy for older patients with hormone receptor-positive early-stage breast cancer who do not receive surgery [6-11].

In line with the suggestion by the International Society of Geriatric Oncology (SIOG) and the European Society of Breast Cancer Specialists (EUSOMA), PET is used for older patients who are unfit for surgery due to physical functioning impairment [12]. The national audit of breast cancer in older patients (NABCOP) in England from 2017 to 2022

reported a growing number of older patients receiving PET rather than surgery, irrespective of whether they were physically fit or unfit for surgery [6-11].

This increasing number of PET used in older patients may be because robust clinical and economic evidence is lacking to inform clinicians' decisions on choosing PET or surgery for older patients [13]. In addition, older patients prefer a less invasive treatment such as PET to surgery [12]. Given the budget constraints under the national health service (NHS) framework, healthcare providers are driven to provide patients with clinically effective and cost-effective treatment [14]. This PhD thesis was motivated by the lack of clinical and cost-effectiveness evidence of PET versus surgery to be informative for clinical guidelines supporting the treatment decision-making for the increasing number of older women with early-stage breast cancer.

1.2 Aims and objectives

This PhD thesis aimed to generate evidence to understand the clinical and cost-effectiveness of surgery compared with PET for older women with ER+ early-stage breast cancer to inform the use of PET and surgery for older women with early-stage breast cancer. The objectives included:

(1) To summarise the current economic evidence and appraise the evidence source used to estimate input parameters (i.e., the natural history of the disease, treatment effects, health state utility values, and resource use and cost) in the published economic evaluations in older women with breast cancer (Chapter 3).
(2) To summarise the health state utility values (HSUVs) of breast cancer in postmenopausal women and identify the association of HSUVs decrements with age increase (Chapter 4).
(3) To evaluate the cost-effectiveness of PET versus surgery in older patients who are physically fit for surgery and the impact of the imperfect implementation of surgery

in England (Chapter 5).

(4) To evaluate the comparative clinical effectiveness of PET versus surgery for older patients unfit for surgery due to frailty or comorbidity, stratified by levels of frailty and comorbidity (Chapter 6).

(5) To evaluate the cost-effectiveness of PET versus surgery in older patients who are pre-frail or frail and the value of further research (Chapter 7).

1.3 Thesis outline

The PhD thesis consists of eight chapters (Figure 1.1). Chapter 2 reports a comprehensive literature review that outlines the challenges of treating older women with early-stage breast cancer, appraises the current evidence of PET versus surgery in older patients with early-stage breast cancer, identifies the clinical and economic evidence gaps, and emerges research questions for this PhD study.

After that, two evidence synthesis chapters are presented. Chapter 3 reports a systematic review to identify published economic evaluations of older women aged ≥ 70 years with early-stage breast cancer to inform the structure of decision-analytical modelling and appraise the evidence sources used to estimate input parameter values. This Chapter has been published in a peer-reviewed journal [15]. To elicit the utility values suitable for older patients, Chapter 4 presents a systematic review to summarise published studies on health state utility values (HSUVs) of breast cancer in postmenopausal women. A meta-regression analysed the age-associated HSUV decrements in older women with breast cancer. The manuscript of this Chapter is currently under peer review for publishing.

Based on the published clinical evidence from randomised controlled trials (RCTs), Chapter 5 reports a model-based economic evaluation comparing the cost-effectiveness of PET versus in patients who are fit for surgery. Besides, a value of implementation

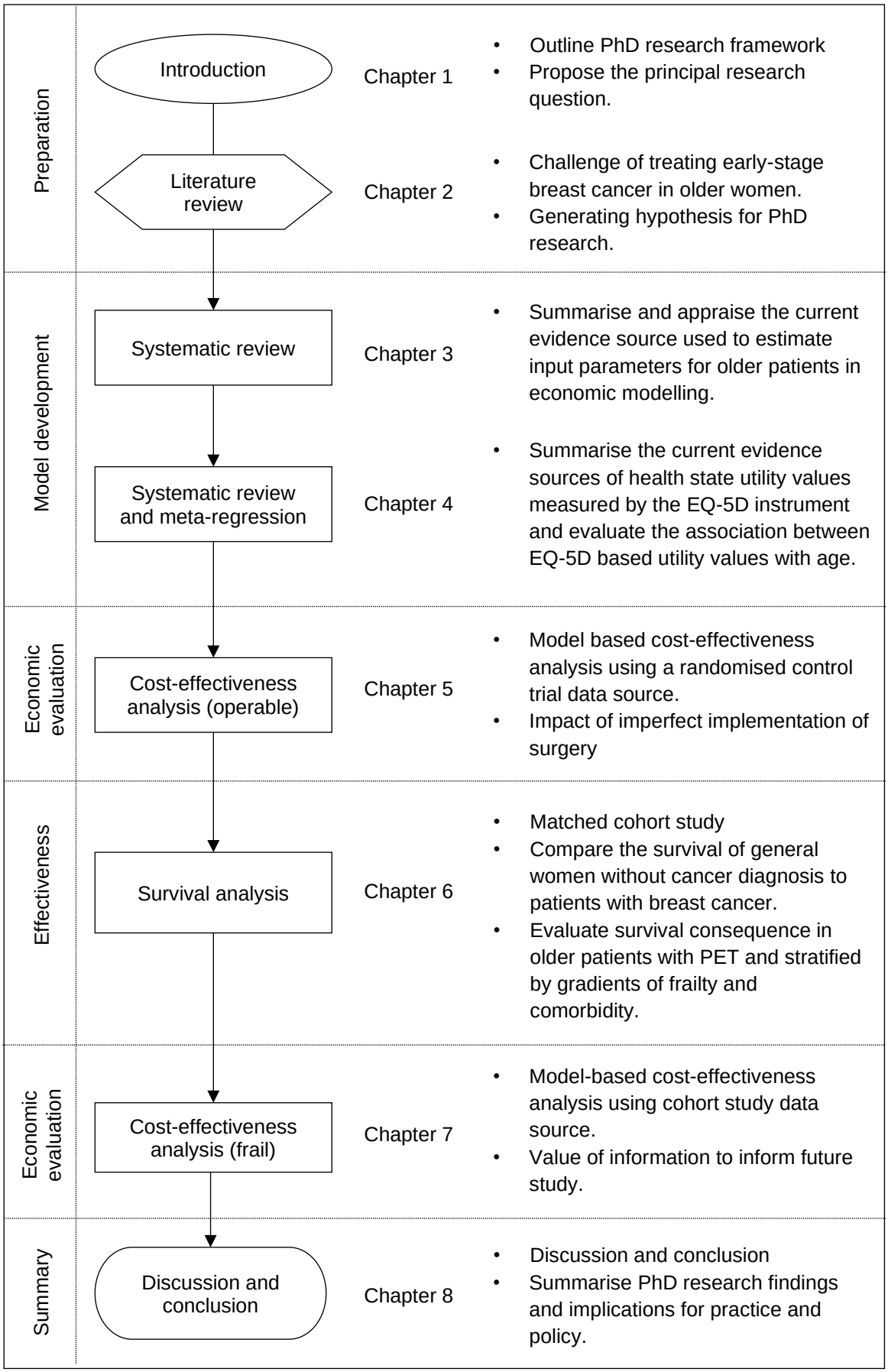
analysis assessed the impact of imperfect uptake of surgery in England. The analysis designated for clinicians and policymakers in England about the cost-effective strategy for older patients and how to strengthen the current guideline in improving healthcare resource allocation. The results of this chapter have been presented at an international peer-reviewed conference and awarded the best poster [15].

Chapter 6 depicts two cohort studies that progressively investigated the clinical and comparative effectiveness of PET versus surgery, considering patients' age, frailty levels and initial treatment strategies (PET or surgery). A matched cohort study compared overall survival between postmenopausal women with a breast cancer diagnosis and those without cancer to investigate the impacts of age, frailty, and comorbidity on survival by two treatments (surgery or PET). Following that, a cohort study compared the overall survival and breast cancer-specific mortality of PET versus surgery in older women with early-stage breast cancer stratified by gradients of frailty (non-frail, pre-frail and frail) and levels of comorbidity (low, intermediate and high levels). This study provided overall survival data for a further economic evaluation (Chapter 7) of PET versus surgery in older women with physical functioning impairment (pre-frail or frail). The results of this chapter have been published as podium [16] and poster presentations [17, 18]at an international peer-reviewed conference.

Chapter 7 presents a model-based economic evaluation and a value of information analysis to evaluate the cost-effectiveness of PET versus surgery in older patients who are pre-frail or frail and the value of further research to resolve uncertainty in the clinical and economic evidence base (the model structure was identical to the one in Chapter 5). The probabilities from stable to dead state of treatments (i.e., surgery or PET) were estimated from the overall survival in Chapter 6. The results of this chapter have been presented in a poster presentation at an international peer-reviewed conference [19]. Finally, Chapter 8 is a concluding chapter summarising the contributions to the PhD

thesis knowledge and discussing the implications for clinical decision-making and policymakers.

Figure 1.1. Conceptual framework and thesis development process



Chapter 2 Literature review

This chapter reviews the literature on emerging challenges and increasing healthcare needs in treating older women with early-stage breast cancer and summarises current evidence in treating early-stage breast cancer in older women. The literature review informed the aim and objectives of this thesis.

2.1 The epidemiology of breast cancer in women

Cancer is one of the most prevalent non-commutable diseases and one of the leading causes of death globally [4, 20, 21]. In 2021, there were 19.3 million new cases and 10 million cancer deaths estimated by the World Health Organization (WHO) [4]. Breast cancer, the most prevalent cancer globally, has a high incidence annually. Breast cancer in females, which accounted for 99% of all breast cancer cases, is the leading group of global cancer in 2020, with an estimated 2.3 million new cases (11.7% of all cancer cases) [4]. The high incidence of female breast cancer means that one in four women in their lifetime will be diagnosed with breast cancer globally [4]. In the United Kingdom (UK), the incidence of female breast cancer is higher than the world average, accounting for 15% of all new cancer cases (2016-2018) [5].

Postmenopausal women aged ≥ 50 years are the highest incidence and prevalence of breast cancer worldwide and in the UK [4, 22]. In England, 8 out of 10 newly diagnosed breast cancer cases happen in postmenopausal women aged ≥ 50 [23]. In addition, due to the ageing population worldwide and in the UK, there is an increasing number of postmenopausal women diagnosed with breast cancer at an older age. According to the report by Cancer Research UK (2016), the annual incidences (per 100,000 population) for the age group of 50-59, 60-69, 70-79, and 80-89 years were 562, 770, 782, and 925 cases, respectively. More than one-third (36%) of all breast cancer cases in the UK are diagnosed at an older age (≥ 70 years) [5]. Consequently, older women have become

the leading group of breast cancer diagnoses in England, which may require more health care.

In addition, the survival consequence of female breast cancer after receiving optimal treatments has been extended markedly, particularly in Western European countries since the 2010s due to the advance in screening, diagnosis, and treatments. According to the Global surveillance of trends in cancer survival (2019) reports, the 5-year survival rate in Western European countries from 2010 to 2014 was 87% [24]. In the UK, according to the Office for National Statistics (ONS), 85% and 75% of women will survive breast cancer for 5 and 10 years or more [25], compared to the 5-year survival rate of other chronic conditions in the UK, such as heart failure (74%) [26], and stroke (64%) [27]. Hence, most clinical oncologists worldwide have widely recognised female breast cancer as a chronic condition requiring long-term healthcare service [28, 29].

According to the WHO, smoking, alcohol intake, unhealthy diet, and physical inactivity are common risk factors for developing cancer [30]. Of these, some are preventable, such as smoking, alcohol intake, unhealthy diet, and physical inactivity, and can be managed by individuals to reduce the risk of cancer (including breast cancer) [31]. According to a randomisation study using UK Biobank, smoking (OR: 1.80, 95%CI: 1.59-2.03) and alcohol intake (OR: 1.94, 95%CI: 1.41-2.68) are positively associated with lung cancer, and also had a positive association with non-site-specific cancers [32]. However, other risk factors may not be controllable by individuals, for example, some primary diseases and hormone levels for hormone-related cancer (i.e., breast, prostate, endometrium, testis, ovary, thyroid and osteosarcoma) [5].

Ageing, however, is an unchangeable risk factor for cancer incidence. WHO reported that people aged 60 and over are the highest age group of cancer incidence (more than 500 cases per 100,000) worldwide [33]. In addition, breast cancer is associated with

specific risk factors such as reproductive history, hormone-replacement therapy, the level of sex hormones at post-menopause, genetic mutations, obesity and family history of breast cancer [34]. Among those specific risk factors, the level of sex hormones at post-menopause is a critical risk factor associated with the incidence of breast cancer. The results showed that premenopausal women had a greater risk of breast cancer than postmenopausal women of an identical age ranging from age 45 to 54 years (RR: 1.43, 95%CI: 1.33-1.52) [35].

In the UK, menopause usually starts at age 45 to 55 years, according to the NHS report [36]. Also, a retrospective cohort study (n=5,113) reported that the median age at natural menopause (n=3,650) was 49.0 years (IQR: 45-51 years) in the UK [37], which aligns with the national statistics showed the average age of menopause is 51 years [38]. Therefore, this PhD thesis used age 50 years as the cut-off age in quantifying the cost-effectiveness between PET and surgery for postmenopausal women (Chapter 5 to Chapter 7) and used 45 years in one systematic review to include as many women in the cohort as possible (Chapter 4).

2.1.1 Healthcare service for breast cancer in England

Breast cancer healthcare service in England is provided by National Health Service (NHS), a government-sponsored universal healthcare system. NHS provides healthcare services for breast cancer in NHS trust foundations (i.e., hospitals or specialist clinics as secondary care settings) or general practitioners (GP, as primary care settings) in England. In the UK, the NICE guidelines are the standard treatment used to claim reimbursement for healthcare procedures in government-sponsored hospitals (NHS trust foundations). The NICE is a national advisory body authorised by the government responsible for population healthcare resource allocation decisions in England, which aims to generate clinical and economic evidence of implemented treatment to inform clinical decisions made by relative stakeholders (e.g., patients, healthcare service

providers, policy-makers and payers) [14]. Therefore, any stakeholders for healthcare services associated with breast cancer in England should abide by the NICE recommendation in their decision-making regarding diagnosis and treatment for breast cancer.

The NICE generates two types of evidence (a) clinical guidelines and (b) guidance for technology appraisal. Both are based on the core principles of providing the best evidence available developed through an open and transparent process involving patients, service providers, health carers and the public [39], but focus on different goals. The NICE guidelines aim to improve clinical decision-making considering clinical effectiveness and cost-effectiveness evidence. The scope of clinical guidelines covers the area of clinical management and procedures, medicine practices, antimicrobial prescribing, public health, and social care based on clinical practices. By synthesising the available evidence with a team, including clinical advisors, systematic reviewers, information specialists, health economics *etc*., the guidelines are developed for related stakeholders. Nevertheless, the NICE guidelines are generally a suggestion and not a compulsory rule [40].

On the other hand, the NICE guidance aims to guide the efficient allocation of health resource use by synthesising the evidence available, which compares the clinical effectiveness and cost-effectiveness of comparators (i.e. current implemented health technologies) and new health technologies, such as medications, procedures, devices *etc*. [39]. The NICE guidance, in general, provides the long-term effectiveness and cost-effectiveness between new health technologies and appropriate comparators with a consideration of the evidence, including epidemiology, clinical evaluation, economic evaluations, expert opinions, manufacturers' submissions, innovation, and equity. The cost-effectiveness adopted NHS and Personal Social Services perspective only with a recommended discount rate for outcomes and cost.

2.1.1.1 Breast cancer diagnosis and treatment principle

Breast cancer, like most cancers in general, may not be diagnosed until symptomatic or through a screening program, as there are no symptoms or minor symptoms initially. In England, women may consult their GP when experiencing breast cancer symptoms, such as lumps in the breast [23, 41]. Once women are suspected of having breast cancer after examination by GP, they will be referred (as an urgent referral) to a specialist breast cancer clinic within two weeks generally to confirm whether it is breast cancer through imaging tests (for example, X-ray or computerised tomography scan) and biopsy [23, 42].

The Breast Screening Programme (BSP) has been provided by NHS since 1988. It aims to diagnose female breast cancer as early as possible to maximise the prognosis by optimal treatment and minimise the influence of daily life from breast cancer [43]. The BSP will invite any women aged in a range from 50 to 70 years to receive mammograms (i.e., medical imaging) every three years in England. Due to the age range of the BSP programme, older women aged ≥ 70 may not be diagnosed with breast cancer until breast cancer-associated symptoms appear. Nonetheless, according to the national statistics in England, most patients with breast cancer aged ≥ 70 years in England are early stages.

Once patients with suspected breast cancer or breast cancer symptoms who were referred to a breast specialist clinic or hospital have confirmed their diagnosis, patients should have a consultation with healthcare professionals to decide their treatment strategy within a specific period [44]. According to the standard of the Care Quality Commission (CQC) England, patients with breast cancer should receive their initial treatment within a certain period [44]. For patients with an urgent suspected cancer referral, referral for breast cancer symptoms, or via cancer screening, cancer treatment should be given within 62-day of that initial referral; or for patients with a confirmed

cancer diagnosis, cancer treatment should be given within a month (31-day) of deciding to treat their cancer [44].

In principle, as a consensus of worldwide breast cancer management, diagnosing and treating breast cancer as early as possible can maximise patients' survival [45]. Besides, surgical procedure is recognised as the primary treatment of operable breast cancer, and additional treatment strategies (e.g., chemotherapy, radiotherapy *etc*.) can be co-applied to maximise the treatment effect [46]. Primary treatment is the first cancer treatment, and surgical procedures to remove detectable cancer from the body have been recommended as the primary treatment to "cure" breast cancer [47, 48]. Any additional treatments before the primary treatment to make cancer operable are defined as neo-adjuvant treatment, which aims to shrink the size of the cancer [49]. In contrast, adjuvant treatments are additional treatments given after primary treatment to reduce the risk of cancer recurrence [47, 48]. Post-surgical adjuvant treatment after surgical procedures is usually given to control undetected cancer, prevent relapse risk, and maximise clinical effectiveness [50]. Cancer stage, grade at diagnosis, and biological characteristics of breast cancer are key factors influencing clinical treatment decisions on providing surgery with neo-adjuvant or adjuvant treatments [11].

Cancer stage and grade associated with treatment decision-making

Both the size of the cancer and whether cancer spreads to nearby tissue or distant organs characterise the 'stage of cancer' at diagnosis [51]. It is a crucial factor influencing treatment strategy selection and whether surgical procedures can be applied. Specifically, breast cancer can be staged according to the tumour node metastasis (TNM) cancer-staging scheme [51]. The TMN cancer-staging scheme comprises three elements: the tumour size (T), lymph nodes state (N) and metastatic states (M). Breast cancer can be categorised into four stages depending on the different statuses of three elements: Stages I, II, III and IV (Table 2.1). Four TNM breast cancer stages differentiate

four types of breast cancer: ductal carcinoma in situ (DCIS), early-stage (Stage I, II and IIIA), locally advanced (Stage IIIB or IIIC) and metastatic (Stage IV) breast cancer depending on whether surgical procedures can be applied [52]. Early-stage, locally advanced, and metastatic breast cancers are invasive breast cancer. They are the primary type of breast cancer, with an average annual incidence of 55,900 new cases from 2016 to 2018, according to national statistics [5]. DCIS is a pre-cancer, operable condition that some cells in the lining of the breast tissue's ducts have started turning into cancer cells [51], and on average, there were 8,300 new cases from 2016 to 2018 in the UK.

Table 2.1. Tumour node metastasis staging scheme for breast cancer

Stage grouping	T stage	N stage	M stage
DCIS / Stage 0	Tis	N0	M0
Early breast cancer			
IA	T1	N0	M0
IB	T0/T1	N1(mi)	M0
IIA	T0/T1	N1	M0
	T2	N0	
IIB	T2	N1	M0
	T3	N0	
IIIA	T0, T1, T2	N2	M0
	T3	N1, N2	
Locally advanced disease			
IIIB	T4	N0, N1, N2	M0
IIIC	Any T	N3	M0
Metastatic disease			
IV	Any T	Any N	M1

(Note) DCIS: ductal carcinoma in situ; Tumour size: Tis: in situ cancer or pre-cancer; T1 = 1-20 mm; T2 = 21-50 mm; T3 = 51+ mm; T4 = tumour spread to skin or chest wall. Nodal status: N0 = no cancer cells in lymph nodes; N1, N2, N3 increasing spread of cancer within the lymphatic system. mi = micro-metastases

Early-stage breast cancer is operable with a smaller tumour size, fewer lymph node involvement and less spread status, which can be removed by the surgical procedure [7]. Locally advanced (Stage IIIB or IIIC) and metastatic (Stage IV) breast cancer that surgical procedures cannot remove can generally be treated with neo-adjuvant treatments to shrink cancer into operable. If these tumours at locally advanced stages

cannot be given surgical procedures from neo-adjuvant treatments, additional treatment (e.g., chemotherapy, radiotherapy *etc*.) are applied to control cancer reproduction and spread to maintain normal daily functioning and quality of life.

In England, early-stage breast cancer is the most common breast cancer. According to the Cancer registration statistics in England (2019), the majority (85%) of newly diagnosed breast cancer was at stage I and II, 10% at stage III breast cancer, and 5% at stage IV [25]. Also, early-stage breast cancer is the most commonly diagnosed breast cancer stage among older women aged ≥ 70 years with breast cancer [11]. For older patients aged ≥ 70 years, nearly 70% of newly diagnosed breast cancer were early-stage breast cancer between 2016 and 2018, according to the National Audit of Breast Cancer in Older Patients (NABCOP) 2022 [11]. NABCOP is a national clinical audit of all NHS hospitals delivering breast cancer care in England and Wales. This audit comprehensively reports the annual information on diagnosis and treatment patterns of breast cancer care for women aged ≥ 50 years. From 2017 to 2019, the audit reported the information stratified by two age subgroups: 50 to 69 years and 70+ years [6-8]; while since 2020, the audit further stratified age into three age groups 50 to 69 years, 70 to 79 years, and ≥ 80 years [9-11].

Cancer grade describes how normal or abnormal cancer cells look under the microscope, which is classified into three levels: grades 1, 2 and 3 [53]. As the grade level rise, the cancer cell grows faster [54]. A higher breast cancer grade means there may be a higher risk of breast cancer recurrence or a poorer prognosis with receiving optimal treatment strategies (i.e. surgical procedures) [54]. Surgical procedure is still the first-line treatment no matter which breast cancer grade is tested worldwide and in the UK. On the other hand, cancer grade generally informs whether adjuvant chemotherapy or radiotherapy should be applied to the patients [3]. In England, Section 2.1.2.2 of the NICE guideline for breast cancer suggests considering the risk of recurrence (i.e., breast cancer grade)

in deciding whether other additional adjuvant treatments (e.g., chemotherapy, radiotherapy, or endocrine therapy) are given to patients with breast cancer [3].

Cancer biological characteristics associated with treatment decision-making

In addition to cancer stage and grade at diagnosis, two vital biological characteristics, i.e., hormone receptor status and proto-oncogene Neu status, influence the treatment decision-making of breast cancer on whether other two breast cancer-specific adjuvant treatments can be applied, i.e., endocrine therapy (ET), and biological therapy (BT).

Female hormones can stimulate breast cancer cells' growth, which can be attached to specific proteins tested in breast cancer cells, and these proteins are named hormone receptors, classified explicitly as oestrogen receptors (ER) or progesterone receptors (PR) [3]. Hormone receptor-positive (+) or hormone receptor-negative (-) breast cancer is classified according to whether the tumours have these receptors. Clinically, hormone receptor-positive breast cancer means breast cancer cells have either ER, PR, or both (hereafter, hormone receptor-positive is referred to as ER+ in this thesis). The immunohistochemistry (IHC) test is often used to detect oestrogen and progesterone receptors in cancer cells. According to the American Society of Clinical Oncology guideline, breast cancer is hormone receptor-positive if at least 1% of cancer cells tested have ER or PR because ‘1% of tumour cells with ER+’ has been demonstrated to correlate with the clinical outcome, i.e., disease-free and overall survival [55].

The IHC method also can quantify the ER+ status as the level of ER+ strength. The level of ER+ strength can derive as a histological score (H-score) or the Allred score in clinical practice [56]. Both of H-score (Formula 2.1) and the Allred score (Table 2.2) are calculated by the percentage and intensity of positive receptors; the H-score ranges from 0 to 300, of which the positivity cut-off by a defined threshold (≥ 100 in generally defined

as ER+), whereas the Allred score ranges from 0 to 8, of which a score above 3 generally is defined as ER+ [57].

H-score = [(0 × N) + (1 × W) + (2 × I) + (3 × S)] **Formula 2.1**

(Note) N: % of no staining; W: % of weak staining; I: % of intermediate staining; S: % of strong staining.

Table 2.2. Allred score interpretation and calculation

Proportion score	Positive cell (%)	Intensity score	Intensity of positivity
0	none	0	None
1	<1%	1	Weak
2	≥1%, <10%	2	Intermediate
3	≥10%, <33%	3	Strong
4	≥33%, <66%		
5	≥66%		

(Note) Allred score= proportion score + intensity score

The level of ER+ strength has been shown to increase with age. A study (2008) reviewed the proportion of women with an H-score over 200 in the different age groups, the proportion of patients with an H-score over 200 in the age groups below 35, 35-50, 50-70, and 70+ years old, were 4%, 5%, 21%, and 42% in patients, respectively [58].

Hormone receptor-positive breast cancer is the leading group of female breast cancer in the UK in all age groups, and 7 out of 10 breast cancers (70%) are ER+ [59]. A cross-sectional study using Scottish Cancer Registry Data identified 72,217 women diagnosed with incident breast cancer between 1997 and 2006, and 76% of patients with breast cancer were ER+ [59]. According to the UK National Audit of Breast Cancer in Older Patients (NABCOP) 2022, 87% of postmenopausal women (aged ≥ 50 years) had ER+ early-stage breast cancer [11]. In addition, the incidence of hormone receptor-positive breast cancer increases with age. A cross-sectional study using the Surveillance, Epidemiology, and End Results in the United States cancer database (SEER) indicated

that the proportion of ER+ and PR+ status increased from 83% and 57% in 55-year-old patients to 91% and 66% in 90-year-old patients, respectively [60].

ER+ breast cancer can be treated with endocrine therapy drugs (ET) as primary or (neo-) adjuvant treatments to block hormones stimulating breast cancer cells [3]. In line with the NICE guideline of breast cancer recommendations, tamoxifen, the most commonly prescribed ET medication in England, is an oestrogen receptor modulator that inhibits the growth of and promotes apoptosis in oestrogen receptor-positive tumours [61]. Aromatase inhibitors are later developed ET medications for 'postmenopausal patients' that can also treat ER+ breast cancer by blocking the production of oestrogen [61]. The ovary is the main organ producing oestrogen for females. It stops producing oestrogen in the post-menopause period, and after that, oestrogen is mainly transferred from peripheral tissues catalysed by aromatase [61]. Therefore, aromatase inhibitors are suitable for inhibiting oestrogen functions in postmenopausal patients.

A meta-analysis of randomised control trials (RCTs) using individual patient-level data evaluated the clinical effect of adjuvant aromatase inhibitor or tamoxifen for postmenopausal for five years in women with ER+ early-stage breast cancer (n=31,920) [62]. The results indicated that, although there was no difference in the 5-year mortality rate between the two treatments (relative risk=0.89, 95%CI: 0.78-1.03； p value=0.11), aromatase inhibitor showed a lower recurrence rate than tamoxifen (relative risk=0.56, 95%CI: 0.46-0.67) [62]. Hence, aromatase inhibitors have better effectiveness in breast cancer treatment (i.e. disease progression) than tamoxifen for postmenopausal women with ER+ early-stage breast cancer [61].

In addition, the levels of ER+ strength in the individual patient differentiate their responses to ET. A review compared ten-year disease-free survival and overall survival for post-menopausal women (n=583) with ER+ positive breast cancer receiving post-

surgical adjuvant tamoxifen alone in the UK [63]. The results demonstrated that ten-year survival rates significantly reduced with the levels of ER+ strength decreased quantified by H-score. The 10-year survival rates were 84%, 71%, 67% and 41% with the H-score of >200, 100-200, 50-100 and < 50, respectively ($p<0.001$); and the figures for ten-year disease-free survival were similar, being 84%, 83%, 73% and 28% for same H-score categories ($p<0.0001$) [63]. Consequently, older women may have a higher proportion of ER+ breast cancer and a relatively higher level of ER+ strength, which leads to a superior treatment effect from ET compared with their younger counterparts.

Furthermore, amplification or over-expression of an inherited faulty gene (oncogene), the proto-oncogene neu, typically called human epidermal growth factor receptor 2 (HER2/neu), plays a vital role in breast cancer [64]. HER2/neu is one of the human epidermal growth factor receptor (HER/EGFR/ERBB) family, a protein encoded by the ERBB2 gene in breast cancer [3]. In recent years, the protein has become an important biomarker and target for biological agents (e.g., monoclonal antibodies) for breast cancer treatment, and a quarter (25%) of breast cancer patients are tested as HER-2 positive [65, 66]. The biological treatment for HER-2-positive breast cancer is generally used as an adjuvant treatment strategy after primary surgery to enhance the survival benefits [65, 66].

Patients with HER-2-positive breast cancer are highly likely to respond to biological agent adjuvant treatment, such as trastuzumab, which improves the prognosis of HER2-positive breast cancer. In a systematic review and meta-analysis of RCTs, compared to standard chemotherapy alone, trastuzumab as an adjuvant treatment of HER-2 positive early-stage breast cancer can significantly reduce the mortality (hazard ratio: 0.63-0.77, $p<0.00001$ by different chemotherapy regimens) and recurrence (hazard ratio: 0.64-0.75, $p<0.00001$ by different chemotherapy regimens) [67]. However, older women with early-stage breast cancer show lower expression of HER2 negative. The proportion of HER2-

positive status reduced from 17% of women aged 55-64 years to 10% of women aged 85+ [68], which means older patients may gain limited benefits from biological agent adjuvant treatment due to a smaller proportion of patients with HER-2-positive breast cancer than their younger counterparts.

2.1.1.2 The NICE treatment guideline for early-stage breast cancer

Considering this cancer stage, grade and biological characteristics associated with treatment decision-making, the NICE recommended prioritising treatment strategies for women with early-stage breast cancer based on the current evidence to maximise the clinical and cost-effectiveness of the population in England. According to the NICE guideline, surgical procedure is the first-line treatment (i.e. primary treatment) for women with early-stage breast cancer (operable breast cancer), irrespective of chronological age at diagnosis, unless patients are physically unfit for surgery [3]. Meanwhile, hormone receptor and HER 2 status are recommended to be assessed simultaneously at the initial diagnosis to inform the benefits and harms of other adjuvant treatments [3].

Initial treatment strategy

The NICE guideline recommends two types of surgical procedures as the primary surgical procedure for early-stage breast cancer, including mastectomy that removes the entire breast, or a less invasive breast-conserving surgery (BCS) that removes part of the cancerous or abnormal breast tissues instead of the whole breast [69]. Breast-conserving surgery as a prioritised recommendation is applied to patients with early-stage breast cancer with no surgical contraindications. Mastectomy is recommended as a different approach for patients with certain types of risks, such as cancer and/or DCIS present at the radial margins after breast-conserving surgery [3]. In addition, breast reconstruction surgery, including immediate breast reconstruction and delayed breast reconstruction, is also provided to patients with mastectomy [3]. In England, delayed

breast reconstruction was the dominant strategy because it has fewer post-complications and will not influence the time of adjuvant treatments applied [70].

Adjuvant treatment strategy

Other treatment strategies, including chemotherapy (CT), radiotherapy (RT), endocrine therapy (ET), and/or biological therapy (BT), were adopted as (neo) adjuvant strategies in England for patients with early-stage breast cancer recommended by the NICE guideline [3]. CT and/or RT are provided to patients with a higher risk for breast cancer recurrence after surgery, for example, grade 3 breast cancer, patients with BCS, or lymph nodal-positive disease. Adjuvant BT, e.g., trastuzumab, is suggested for patients with Stage T1c and above with HER2‑positive breast cancer for one year in combination with surgery, chemotherapy and radiotherapy as appropriate [3].

ET is suggested as the first-line adjuvant treatment for ER+ breast cancer for 2-5 years [3]. Tamoxifen as the initial adjuvant ET is given to men and premenopausal women, and aromatase inhibitor as the initial adjuvant ET is given to postmenopausal women at medium or high risk of disease recurrence [3]. An extended ET (aromatase inhibitor) was provided to postmenopausal women at medium or high risk of disease recurrence (people who have lymph node‑positive breast cancer, with tumours that are T2 or greater, and higher grade [3].) and who have been taking tamoxifen for 2 to 5 years with a total duration of more than five years, as recommended by the NICE guideline [3].

2.1.2 The clinical decision-making process in treating breast cancer

In England, the NICE recommends a shared decision-making (SDM) process in treatment decision-making by clinicians and patients [36], which brings patient preference and evidence-based clinician advice together in making the most appropriate treatment decision for the individual patient to maximise the treatment benefit. In other

words, clinical decision-making in England is a co-decision strategy on patient preference and clinician advice. Specific to breast cancer in older women, patient preference and clinician advice are the key factors in the decision-making process. There was a survey that investigated preferences for breast cancer treatment decision-making for older women with breast cancer (n=101, aged from 75 to 99 years) in England (2017) [71]. The results indicated that the main models of decision-making processes in England were patient-centred decision-making (36%), doctor-centred decision-making (35%) process, and SDM (22%) [71].

Besides patients' self-preferences in treatment decision-making, evidence-based information provided by healthcare professionals plays a vital role in facilitating patients to make the most appropriate treatment decisions. The clinician will provide clinical treatment suggestions to their patients based on evidence-based clinical guidelines, medical experience, and self-preference attempts to maximise treatment effects and minimise side effects. In the UK, the NICE guidelines are the standard treatment used to claim reimbursement for healthcare procedures in government-sponsored hospitals (NHS trust foundations). Hence, the NICE guideline for breast cancer was the standard clinical practice in selecting treatment strategies for any breast cancer patient in England (Section 2.1.2.2). Consequently, any clinical advice provided by healthcare professionals should be based on the NICE guideline in England and consider patient preference and whether patients' physical conditions fit the standard treatment strategy recommended by the NICE guidelines.

2.1.3 Routine clinical practice in treating older women with early-stage breast cancer

Despite the surgery being suggested as a first-line treatment strategy irrespective of age for women with early-stage breast cancer, the treatment strategy of breast cancer routinely varied by age. The National Audit of Breast Cancer in Older Patients (NABCOP)

2022 reported that 97% of younger women aged 50-69 years with early-stage breast cancer (n=94,044) received surgery, while 78% of older women aged ≥70 years (n=56,245) received surgery [11]. For ER+ early-stage breast cancer, 97% of younger women aged 50-69 years received surgery (n=81,649), while 76% of older women aged ≥ 70 years received surgery (n=48,839) [11]. Of the older patients with ER+ early-stage breast cancer not receiving surgery (n=11,744), 92% received primary endocrine therapy (PET) as the initial treatment.

Nonetheless, the surgery rate for older women with early-stage breast cancer has increased recently. According to the NABCOP [11], the surgery rate for older women over 80 years with early-stage breast cancer who were fit or had mild-moderate frailty rose from 62% in 2014 to 72% in 2019. There were 5% and 32% of surgery-fitted older women aged 70-79 and over 80 years who did not have surgery as primary treatment [11]. In addition, there was a significant variation in the surgical rate in different hospitals in England, as reported in NABCOP [11]. Although there may be reasonable reasons for the omission of surgery for older patients in hospitals, this significant variation in surgical rate indicated a lack of consensus or guidelines to guide PET utilisation in clinical and cost-effective approaches. Consequently, PET has become a common alternative treatment strategy to surgery for older women aged ≥ 70 years with early-stage breast cancer in England [11].

2.1.4 Factors associated with primary non-surgical treatment for older patients with early-stage breast cancer

Older women aged ≥ 70 years have been the leading group of PET utilisation to the report of NABCOP in England (Section 2.1.4). According to the latest recommendation of the European Society of Breast Cancer Specialists (EUSOMA) and the International Society of Geriatric Oncology (SIOG) 2022 for the management of older patients with

breast cancer [12], PET is recommended only for patients with ER+ breast cancer, and have a shorter expected life expectancy (less than three years).

According to the clinical perspective and suggestion, besides patient preference, two key components may be associated with the PET used as an alternative to surgery for patients with early-stage breast cancer: (1) ER-positive breast cancer, which is the basis of ET; (2) shorter life expectancy, which characterises patients who are less likely to receive surgery as primary treatment. The challenge of PET utilisation is characterising patients with a shorter life expectancy. Other competing risks of death may cause a shorter life expectancy for patients with breast cancer, for example, frailty and cerebrovascular or cardiovascular diseases [72]. Hence, besides the impact of patient preference and biological characteristics on treatment decision-making of PET, the distinct physical functioning of older women with breast cancer are the key factors driving PET utilisation.

Physical functioning is usually associated with frailty and comorbidity for the older population during treatment decision-making of cancer [73, 74]. Generally, frailty is the aggregation of sets of physiological conditions, leading to a heightened vulnerability in stressful situations (e.g., invasive or high-intensity treatment for cancer) [75]. Briefly, frailty is a state of extreme vulnerability to stressors that leads to adverse health outcomes. In clinical practice, frailty is often used to evaluate the risk of post-surgical complication incidence, intolerance of chemotherapy and radiotherapy, disease progression and short-term (within three months) mortality [74]. Clinically, the activity daily living score was used to measure frailty worldwide and in England [74]. Also, other algorithms were developed using diagnosis codes to estimate frailty in England, for example, hospital frailty risk score [76].

Comorbidity is more than one additional condition co-occurring with a primary condition (e.g., cancer) [77]. Comorbidity, in clinical, is often used to evaluate cancer treatment selection, intolerance of chemotherapy and radiotherapy, and long-term (general 10-year) mortality [73]. Charlson Comorbidity Index (CCI) has been commonly used to quantify comorbidity levels to inform treatment decision-making [78], which included 19 conditions assigned with different weights to indicate the severity of comorbidity and long-term (10-year) mortality risk.

Frailty and multiple comorbidities are often associated with ageing, and older patients are highly likely to be unfit for surgery due to frailty and comorbidity [74]. Specific to treatment decision-making for older women with early-stage breast cancer, a prospective cohort study across 51 hospitals in England [74] evaluated the factors associated with the treatment decision of PET or surgery for older women aged ≥ 70 years with ER+ early-stage breast cancer (n=1,122) [79]. In this cohort study, there was 78% of patients (n=880) received surgery, and 22% of patients (n=242) received PET [79]. The cohort study assessed factors associated with such treatment decision-making, including age at diagnosis, comorbidity using modified Charlson Comorbidity Index (CCI), and frailty using activities of daily living (ADL) score, Mini-Mental State Examination (MMSE) score, HER2 status, tumour size, grade and nodal status [79]. The results indicated that age was the significant factor influencing the treatment decision-making for surgery, with a median age of 84 years for PET and 76 years for surgery [79]. In addition, the late stage of breast cancer diagnosis (i.e., tumour size), reduced functional ability (lower ADL score), and increasing comorbidity (higher CCI) were associated with a potential increase of the likelihood of PET for older patients [79].

Although there was no consensus on the cut-off line for defining ‘older age’, from a clinical perspective, the term ‘older patients’ generally is associated with patients with

poorer physical functioning. An international survey of 288 oncologists across 28 countries agreed that 70 years is an appropriate cut-off age to define patients as older due to their physical functioning impairment [80]. Moreover, expert opinion was also referred to in this thesis to define the age of an older patient with physical functioning impairment (Professor Cheung Kwok-Leung in Royal Derby Hospital Centre England, a surgeon consultant, as the advisor in the thesis on the clinical issues and definition). Therefore, patients aged ≥ 70 are defined as 'older patients' in this thesis because they are less likely to receive identical treatment strategies to their younger counterparts (i.e., surgical procedures) by functioning impairment or disability.

In addition to age-associated comorbidity and frailty factors, older patients' preferences may also influence treatments provided to older women with ER+ early-stage breast cancer. According to a survey in England, semi-structured interviews were undertaken with older women (n=33, median age= 82, range 75-95 years) with breast cancer [81]. They found that older patients prefer less invasive treatment strategies (i.e., non-surgical procedures) with minimal influence on their quality of life [81]. Besides, a questionnaire survey of healthcare professionals in the UK (including 20 breast surgeons, 13 nurse specialists, and one geriatrician) was carried out to investigate clinicians' decision-making in selecting treatments for older women with ER+ early-stage breast cancer [82]. The survey showed that patient preference is crucial when considering treatment. In addition, a quarter (26%) of interviewees agreed that PET might be offered to any older women with ER+ early-stage breast cancer because there was a lack of evidence indicating survival benefits from surgery [82].

Consequently, one of the critical challenges in treating older women with ER+ early-stage breast cancer is the lack of clinical and cost-effective evidence between PET and surgery to inform clinical decision-making by clinicians and patients efficiently.

2.1.5 Clinical and economic evidence of primary endocrine therapy versus surgery

According to the NICE guidance, any treatment provided in England should be based on clinical and economic evidence [83]. A systematic review and meta-analysis of effectiveness derived from well-designed high-quality RCTs or observational studies are considered robust evidence to inform clinical efficacy and effectiveness between treatments [83]. Clinical efficacy refers to the clinical effects of an intervention compared with a placebo in experimental studies (i.e. in an RCT) of a specific group of patients with identical features [84]. Clinical effectiveness refers to the comparative clinical effects of an intervention compared with other alternatives for patients with various features in the real world [84]. Economic evaluations compare the cost-effectiveness of alternative strategies compared with standard health technologies [85] to support treatment decision-making under the limited healthcare resource [86]. This section summarises the current knowledge from RCTs, observational studies, systematic reviews of RCT or observational studies, and economic evaluations comparing PET versus surgery in older women with early-stage breast cancer.

RCTs and observational studies are commonly applied to infer the potential causal relationship between the exposures and outcomes. However, some measured or unmeasured confounding factors could introduce confounding, a systematic error in causation [87]. Specifically to the thesis, some confounders may influence the causal relationship inference between the treatment and survival. For example, physical functioning is a confounder that may influence the treatment selection and survival consequence, and age is another confounder that may influence physical functioning. The most concerning confounders in the thesis were age, physical functioning, frailty, comorbidity and any information that may influence the surgery possibility because different initial treatment strategies (i.e., surgery or PET) may be interfered with by the clinicians' judgement of patients' characteristics (which may be subjective) [88].

Therefore, the outcomes may be confounded by patients' characteristics instead of influenced by treatment strategies alone.

In addition, there also are biases induced during the data collection and analysis process. There are two main types of bias in research: selection bias and information bias [87]. In this thesis specifically, selection bias may be introduced by the difference in treatment selections by clinicians who will subjectively select a treatment that fits the physical functioning of patients due to frailty or comorbidities [88].Misclassification bias in the thesis may focus on the patients who received PET as the initial treatment strategy, of which the role of this strategy aimed to shrink the tumour for the following surgery. Such patients may be misclassified into the PET group [89].

Specific study designs or analytical procedures can control the confounding. For example, randomised control trial is an experimental study designed to infer the causal relationship between exposures and outcomes by randomising treatments to effectively avoid the selection bias at the beginning of the study [90]. RCT has good internal validity (i.e., reliable and trustworthy causal relationship) to assess the efficacy or effectiveness of a target intervention compared with a placebo or standard treatment [91] by imposing randomising participants who are recruited by the stringent inclusion and exclusion criteria balance study population feature to minimise confounders [92]. In addition, restriction, including sampling and matching, is another common design approach in routine analysis to address several confounders [93]. This approach needs a large enough population to develop the appropriate matching procedure. If multiple confounding factors need to be matched, it is not easy to find a suitable match. Once the factors are selected as the matching variables, they cannot be evaluated as risk factors [93].

Furthermore, statistical methods, including stratification and statistical modelling, are often used to further control confounding if appropriate study designs cannot manage it. Regression, a mathematical process to estimate the independent association between many exposure variables and an outcome variable, is the most popular analytical approach to minimise confounding factors [93]. The causal relationship can be estimated once the confounders are included as covariates in the regression process. Stratification is a way of stratifying or putting into categories or levels the exposures or outcomes by included confounders. The advantage of stratification is that this approach can preserve study power and maintain generalisability, but its disadvantage is to deal with multiple confounding factors simultaneously, particularly losing its effectiveness for continuous variables [93].

2.1.5.1 Clinical trials and relevant synthesised evidence

A Cochrane systematic review of RCTs conducted in 2014 synthesised the clinical effects between PET and surgical procedures (i.e., surgery alone or surgery plus post-surgical adjuvant ET) in older women with early-stage breast cancer [94]. Of six RCTs identified [95-105], all the RCTs recruited older women aged ≥ 70 years with pre-defined clinically operable breast cancer who were physically fit for surgery. All the RCTs were not blinded due to the two interventions (surgery and medication), and overall survival and progression-free survival were evaluated as the outcome measures [94]. Except for one study [104], the ER status was not tested in five studies [95-103] because the RCT conducted predated the ER status test recommended in the guideline.

The results of the systematic review [94] indicated that there was no statistical difference in overall survival of PET compared to surgery alone (HR: 0.98, 95%CI: 0.81 to 1.20, p=0.85, three trials of 495 participants) or surgery plus adjuvant ET (HR: 0.86, 95%CI: 0.73 to 1.00, p=0.06, three trials of 1076 participants). Surgery alone or plus adjuvant ET had significantly superior progression-free survival to PET [94]. Of the study for ER+

patients, there was no significant difference in 10-year survival between PET and surgery plus adjuvant ET (HR: 0.80, 95%CI: 0.28 to 2.32; P=0.68) [104]. Therefore, PET was considered non-inferior clinical effects compared to surgery alone or plus adjuvant ET in older women with early-stage breast cancer.

According to the previously published RCTs identified from the systematic review [94], there is a lack of RCTs stratifying participants by physical functioning (i.e., levels of frailty or comorbidity). RCTs usually exclude older patients because older populations have a higher risk of mortality and treatment side effects due to comorbidity and frailty [106, 107] and hence introduce potential bias (for example, selection bias, misclassification bias or immortal time bias) and reduce the reliability of the results [106, 107]. Nonetheless, conducting RCTs to evaluate the treatment effects between surgery and PET-stratified patients by physical functioning is challenging. One RCT attempted to stratify the health status of participants, and it failed to recruit sufficient participants due to a lack of patient recruitment [108]. Therefore, there is still a lack of evidence to indicate the clinical effectiveness and comparative effectiveness of PET versus surgery in older women with early-stage breast cancer who are unfit for surgery due to frailty or comorbidities.

2.1.5.2 Observational studies and relevant synthesised evidence

Since there is a lack of RCTs evaluating the clinical effectiveness and comparative effectiveness between PET and surgery in older women with early-stage breast cancer who are unfit for surgery due to frailty and comorbidity, observational studies are valuable evidence sources to inform the clinical effectiveness and comparative effectiveness [109]. Observational studies have been recognised as having great external validity to generalise the findings of a study to other situations, people, settings and measures because observational studies include individuals in their natural setting receiving various interventions [110].

A systematic review (2014) summarised observational studies to assess the comparative clinical effectiveness between PET and surgery for older patients with an average age of ≥ 70 years [111]. Of 31 cohort studies identified, some studies included patients solely with ER+ (n=12), patients with ER+ and ER- (n=12), and patients who did not test ER status (n=7) [111]. Due to the significant variation in the follow-up period across the studies (ranging from 1 to 202 months), it is not easy to synthesise the survival outcomes [111]. The results indicated that surgery had superior disease control to PET and may have a survival benefit in patients with a predicted life expectancy of five years or more [111].

Also, some observational studies evaluated the effects of PET versus surgery [112-118]. Two large cohort studies compared outcomes in patients with surgery versus PET [112, 113]. Ali *et al.* (2011) reviewed the outcomes of 14,048 women aged > 50 years with breast cancer using cancer registration data from the Eastern Cancer Registration and Information Centre between 1999 and 2007 [113]. They found that surgery had superior overall survival than PET, but a strong selection bias was associated with using PET for older and frailer patients. Similarly, Morgan *et al.* (2015) analysed the data of 17,129 women aged 70 years from 2002 to 2010 in the UK [112]. They found that surgery had superior overall survival, and PET was highly likely to be given to patients with higher stages of breast cancer and more comorbidities [112]. In addition, although these observational studies attempt to use a regression model estimating the survival outcomes by adjusting for the physical functioning (i.e., CCI or ADL) as covariates, the selection bias to PET for older patients was still one potential confounding to influence the outcome.

Consequently, the current clinical evidence showed a similar overall survival benefit comparing surgery versus PET in older women with early-stage breast cancer who are physically fit for surgery. This result may reflect the preference of patients and clinicians

in treatment decision-making of PET for older women with early-stage breast cancer in England. However, there is potential confounding in the current studies to influence the estimation of survival outcomes between surgery and PET for older women with ER+ early-stage breast cancer who are unfit for surgery due to physical functioning. Considering the limit of RCT in older patients, large-scale observational studies using data links in England are a feasible approach to evaluate the clinical effectiveness of PET versus surgery with further adjustment for the selection bias.

2.1.5.3 Economic evidence

The rapidly increasing healthcare cost in the UK is a hot topic of political debate and on the government's public health agenda. According to the ONS report, total healthcare expenditure increased by 4% between 2018 and 2019, with £225.2 billion in government-financed healthcare expenditure in 2019 [119]. In the UK, the government is the leading healthcare funder in England (79%), and the most significant expenditure on healthcare funded by the government in 2019 was secondary healthcare (hospitals), accounting for 48% of overall government healthcare expenditure [119]. Under this increasing economic burden of healthcare needs, it is necessary to allocate the health resource efficiently to improve the healthcare service of breast cancer management in England.

There is an increasing economic burden on older patient healthcare services in the UK due to the increasing need for healthcare for the older population. According to the King's Fund report, there was £22.7 billion spent on adult social care by local authorities in 2018 and 2019, up more than £0.5 billion from 2017 to 2018 [120]. Of this expenditure on adult social care, under a half was spent on working-age adults, with the remaining on people aged 65+ years [120]. For older people, 65% of expenditure was physical support, including medical care [120]. In 2018/2019, there were 1.9 million requests for support from a new client in local authorities, and 1.4 million were from older people [120]. Consequently, as there is a rising economic burden on healthcare for older women with

breast cancer in England, it is necessary to allocate the healthcare resource efficiently to maximise the health benefits for the population based on the economic evidence.

The healthcare expenditure for breast cancer contributes significantly to the economic burden in England due to the highest incidence and prevalence of breast cancer. The cost of breast cancer care is highly related to the age and the stage of breast cancer at diagnosis. In the year of diagnosis, average breast cancer treatment costs are higher in younger than older patients. A retrospective cohort study using Hospital Episode Statistics England estimated the total costs of breast cancer treatments in England for 359,771 patients aged 18-64 years (56.7%) and ≥ 65 years (44.3%) at different stages of breast cancer between 2001 and 2010. Incidence costs in the first year of diagnosis are noticeably higher in patients aged 18 to 64 (£11,109 per patient) than those aged ≥65 (£7,788 per patient) because older patients may be less likely to receive surgery as the initial treatment. The cost of stage I-II breast cancer for patients aged 18 to 64 (£10,746) was higher than the cost for patients aged ≥ 65 years (£7,597); similarly, the cost of stage III-IV breast cancer for patients aged 18 to 64 (£13,315) was higher than the cost for patients aged ≥ 65 years (£8,804) [121]. Also, this study indicated that average cost decreased with the increase of multiple comorbidities ($p<0.001$) [121], as older women are less likely to receive surgery and thus would incur lower costs during the initial year following diagnosis as compared to the younger population.

Besides, surgery was suggested to be one of the main cost drivers for primary breast cancer treatment [122]. Although the average cost of breast cancer treatment in older women may be lower than in their younger counterparts in the first year of diagnosis, the total breast cancer treatment cost in older women with breast cancer is increasing due to the growing ageing population and the higher incidence and prevalence of breast cancer. Under the current budget constraints in the NHS, it is necessary to provide cost-effective treatments to ensure the efficiency of healthcare resource use.

Currently, only one economic evaluation compared the cost-effectiveness of PET with surgery for older women aged ≥ 70 years with early-stage breast cancer in the UK. The economic modelling evaluated the cost-effectiveness by different age groups at diagnosis (70-, 80- and 90+ years), lymph node status (lymph node involvement, yes or no) and comorbidity score (0, 1, 2, 3+, being CCI score). The results indicated that surgery is the cost-effective strategy compared with PET, except for patients aged 90+ years with CCI>1, irrespective of lymph node involvement. However, comorbidity is one of the indicators to assess physical functioning. More economic evaluations are still needed to evaluate the cost-effectiveness for older patients by frailty levels to inform other treatment decision-making. In addition, despite surgery as a cost-effective strategy, many older patients were physically fit for surgery and did not receive surgery (Section 2.1.4). This omission of surgery will lead to a health forgone. Thus, economic evaluations are also required to quantify the health forgone from PET to inform the healthcare strategy improvement that increases surgery uptake for older patients who are fit for surgery in line with the NICE guideline.

2.2 Generating economic evidence to inform decision-making

Decision-makers are challenged to efficiently allocate and utilise healthcare resources to maximise population health under prevailing resource constraints [86, 123-126]. The opportunity cost of health technologies is a critical consideration from the economic perspective during decision-making. Health technology is an intervention, including a test, device, medicine, vaccine, procedure, program or system *etc*., developed to prevent, diagnose or treat medical conditions, promote health, provide rehabilitation, or organize healthcare delivery [127]. For allocating resources to recommend a specific health technology in the NHS, the opportunity cost can be expressed as the health benefit foregone because of adopting a recommended specific alternative [123, 124].

The UK NICE uses economic evidence to explicit the expected opportunity cost of any decision [86]. In the UK, economic evidence of implemented health services must be incorporated into clinical guideline development to improve efficient health resource allocation [125]. Economic evaluation is a primary method of economic evidence, which is defined as "*a comparative analysis of alternative courses of action in terms of both their costs and consequences*" by Drummond *et al.* (2015) [86]. Economic evidence can inform how to improve the technical efficiency of specific health technologies or enhance the allocative efficiency of population healthcare resources based on evaluating whether the expected benefit of the alternative exceeds the opportunity cost [124, 126]. Therefore, evidence from the economic evaluation of alternative health technologies (i.e., PET) is crucial in influencing the decision-making of clinicians, patients and policy-makers.

2.2.1 The method of economic evaluation

Before undertaking an economic evaluation, the first step is conceptualising the decision problem. Conceptualising the decision problem is a process to convert the health process or decision to a representation of the problem, i.e., an explicit statement of the resource allocation decision based on considerations [128]. Three predominant economic evaluation methods inform an explicit decision problem regarding defining characteristics (Table 2.3).

Table 2.3. Defining characteristics of three methods of economic evaluation

Economic evaluation method	Valuation of cost	Valuation of health consequences
Cost-effectiveness analysis (CEA)	Monetary unit	Simple disease-specific outcomes
Cost-utility analysis (CUA)	Monetary unit	Generic measures of the quality of life
Cost-benefit analysis (CBA)	Monetary unit	Monetary units

(Note) cited from Drummond et al. (2015) [86]

Two key elements are involved in any of three methods of economic evaluation: health consequence and cost. The cost calculation included in the three methods are all

monetary units and consists of two components an estimated quantity of resources and a price at which those resources are valued [86]. The incremental cost is the difference in cost between two alternative health technologies (i.e., surgery and PET in this thesis). Three major cost categories are involved in the economic evaluation (Table 2.4). The scope of different categories included in the economic evaluation is decided from the economic evaluation perspective. For instance, only direct medical costs will be included in an economic evaluation from a healthcare system perspective, and a broader set of costs will be included in an evaluation from a societal perspective [129].

Table 2.4. Categories of cost in health economic evaluation

Categories	Component
Direct cost	Direct healthcare resource use related to disease, illness and treatments
Indirect cost	Losses incurred by society from the impact of disease, illness and treatments
Intangible cost	Losses from the impact on quality of life resulting from illness, poor health and their treatments (for example, suffering, anxiety, distress)

(Note) collated from Weinstein (1990) [129]

Under the objective of health maximisation, health's value must be judged. How health should be measured and by whom the health should be valued are the critical elements during the health valuation [130].

A cost-benefit analysis values the benefit of health technology in monetary units. The monetary units as health benefit outcomes in CBA are consistent with the welfarist economic theory that the health benefit should be involved in the entire social welfare to be measured comprehensively [131]. In contrast, a cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) value the benefit of health technologies in health-related outcome measures. These outcome measures are consistent with an extra-welfarist evaluative framework; the health system should be considered independent to trade off the benefit from alternative health technologies [132].

In a CEA, since the natural disease outcome measures are used as a health outcome, it is challenging to compare the health benefit across different types of disease if two disease measures have different outcomes [86]. For example, blood pressure measures are used for hypertension, while blood glucose measures are used for diabetes. Hence, considering that most health technologies affect survival and health status, a generic outcome measure for health must incorporate both quantity and quality of life to make different diseases comparable [86]. In general, cost-effectiveness analysis (including the CEA and CBA) is used as a common nomenclature for an economic evaluation instead of a specific analytical technique by measuring health outcomes in quality-adjusted life years (QALYs) recommended by the NICE guidance [133].

QALYs are calculated by each life year multiplied by the weighting representing the quality of life [134]. The weight measured the total satisfaction or benefit of the current health state, termed utility values. The utility value is assigned from 1 (full health) to 0 (dead), and a health state worse than death is assumed to be possible [86]. Utility values can be measured using different methods, including direct methods (for example, standard gamble, time trade-off, and visual analogue scale) and multi-attribute health status classification systems with preference scores [86]. For example, EQ-5D [135], Short Form Six Dimensions (SF-6D) [136], and Health Utility Index (HUI) [137] are three generic multi-attribute instruments to measure the health state [86].

In addition, the target population (e.g., patients, clinicians, the general population, or healthy ones using a specific health scenario) from which utility values are elicited is crucial for an economic evaluation because the values may vary significantly from the different populations. Utility values elicited from the general population are the recommended health state weights to estimate QALY to ensure that desirable health

states receive a higher weight [86]. The incremental benefit is the difference in QALYs between two alternative health technologies (i.e., surgery and PET in this PhD project).

Cost and QALYs are conventionally discounted because discounting in economic evaluations includes pure time preference [86], a widely observed empirical phenomenon [138]. The discounting will imply that the present value of costs and health outcomes derived in the future will be less than when they are realised.

2.2.2 The standardisation of economic evidence

To maximise population health under the constrained NHS budget for health care, the NICE appraises the clinical effectiveness and cost-effectiveness of health technologies [139, 140]. The standardisation of the method for performing economic evaluation can promote comparability between evaluations. The NICE provided a reference case in England that typically represents a decisionmaker's specific value judgements (Table 2.5) [83].

The NICE reference case applies pre-specified preferred criteria for undertaking an economic evaluation [83]. In the NICE reference case, QALY is an appropriate outcome measure of health benefit. EQ-5D three levels can be used as a preferred instrument to measure the quality of life, and the UK population tariff is a preferred set to value the quality of life. Costs should relate to NHS and personal social services resources. They should be valued using the prices relevant to the NHS and personal social services, and productivity costs and costs not reimbursed by the NHS or social services are not included in economic evaluations for the NICE. A discount rate of 3.5% per year is currently recommended for both cost and QALY. The economic evaluation conducted in the thesis project (Chapters 5 and 7) conformed to the NICE reference case to generate evidence relevant to decision-makers in England.

Table 2.5. Summary of the NICE reference case.

Component of Economic Evaluation	The NICE reference case
Defining the decision problem	The scope developed by the NICE guidance
Comparators	As listed in the scope developed by the NICE guidance
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers
Perspectives on costs	NHS and Personal & Social Services
Type of economic evaluation	Cost-utility analysis with fully incremental analysis Cost comparison analysis
Time horizon	Long enough to reflect all-important differences in costs or outcomes between the technologies being compared
Synthesis of evidence on health effects	Based on systematic review.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers
Sources of preference data for valuation of changes in health-related quality of life	Representative samples of the UK population
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit
Evidence of resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS
Discounting	The same annual rate for both costs and health effects (currently 3.5%)
Handling of Uncertainty	Probabilistic sensitivity analysis is preferred

(Source) National Institute for Health and Care Excellence [83]

(Note): NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, a standardised instrument for measures of health outcome.

2.2.3 Decision-analytical modelling

Two approaches are available to undertake an economic evaluation depending on the data sources used for the economic evaluation: (1) economic evaluation alongside a

single study (an RCT or an observational study); (2) economic evaluation based on a decision-analytic model. The model-based economic evaluation is the most popular approach to conducting economic evaluations [141]. Economic evaluations alongside an observational study or RCT are only applicable if all the key parameters exist and comparator strategies and follow-up duration can be obtained from one source [142]. The model-based economic evaluation allows combining data from different sources when input parameters cannot be obtained from one data source [142]. Model-based economic evaluations can also extrapolate outcomes over a longer time horizon to measure all relevant costs and health events of interest [142]. The NICE guidance suggested that a cost-effectiveness analysis could be modelled around a single well-conducted randomised controlled trial or using decision-analytic techniques with probability, cost and health outcome data from various evidence sources [83].

An analytic decision model represents the progression of a patient's disease and the impact of treatment on disease progression reflected by a mathematical relationship [143]. Based on the different decision problems, several model structures can be used in analytical models, representing the relationship between input and output measures in the modelling [144] (Typical model structures were reported in 0). The input parameters of an analytic decision model are the specific inputs estimated or elicited from various evidence sources [145]. Different types of input parameters for an analytic decision model can be estimated from potential sources of evidence (Table 2.6) [146]. The output of a decision-analytic model is presented as the expected outcomes, such as mean cost and QALYs for each alternative comparator strategy [142]. Decision trees, Markov models, and discrete event simulations of individual patients were the most frequently used model types observed from previously published literature[142, 144, 147] (Appendix 2). The selection of the decision-analytical model and its structure should be justified by a transparent and explicit conceptualisation process [128].

Table 2.6. Example input parameters and source of evidence for a decision-analytical model

Model input parameters	Potential sources of evidence
Clinical effectiveness	Randomised controlled trial; meta-analysis
Natural history of the disease	Observational cohort study.
Resource use	Micro-costing study; direct observation; clinical guidelines
Unit cost	National price lists.
Health-related quality of life	Published databases; mapping algorithms.

(Source) Adapted from Zechmeister-Koss et al. (2014, p.293). [146]

According to the NICE reference case, a systematic review is recommended as the evidence source of clinical effectiveness between comparators and intervention in the economic evaluation because a systematic review of high-quality RCTs can synthesise the results from different studies to increase the sample size to strengthen the statistical power and provide reliable results [83]. This is because RCTs provide a high level of internal validity assessing intervention efficacy to minimise the selection bias by randomisation and homogenise the patients' characteristics between different treatment comparators [86]. However, there are some caveats associated with RCTs which limit their generalisability, such as short follow-up durations, restricted patients' characteristics (excluding the patients with particular specific physical functioning, for example, frailty or comorbidity), failing to present all the relevant comparators in clinical practice, and failing to include the costs and outcomes associated with patients in the clinical practice (protocol-driven costs) [86].

Due to the limited RCTs that stratify participants with breast cancer by their levels of frailty [108], instead, observational studies may enhance the generalisability of results by including patients with specific characteristics (i.e., frailty or comorbidity) to represent the actual health gain and resource utilisation that occurred in the clinical practice. Considering observational studies have less reliable internal validity, the NICE guidance suggested using observational studies as the evidence source when there is a lack of

high-quality evidence sources (meta-analysis of RCTs, RCTs) and adjusting the potential bias [125]. Several analytical methods can be used to adjust the confounding. For example, propensity score weighting (inverse probability treatment weight) is a widely accepted approach used to adjust the selection bias of exposures by related confounders [148].

2.2.4 Decision rules for relative cost-effectiveness

Three outcome measures can be equivalently used to judge the decision rules to inform whether a treatment strategy is relatively cost-effective to an alternative strategy [149]. The decision rules report in Table 2.7.

Table 2.7. Decision rules for relative cost-effectiveness

Decision rules	Definition
$\frac{\Delta c}{\Delta h} < \lambda$	The ratio between incremental costs and incremental health benefits is less than the cost-effectiveness threshold.
$\Delta \mathrm{h} \cdot \lambda - \Delta c > 0$	The incremental net benefit (represented by monetary benefit) is greater than 0.
$\Delta \mathrm{h} - \frac{\Delta c}{\lambda} > 0$	The incremental net benefit (represented by health benefit) is greater than 0.

(Source) Adapted from Claxton et al. (2010; pp.16-17) [149]; Note Δc= incremental cost; Δh= incremental health benefits; λ:cost-effectiveness threshold.

The ICER is the ratio of incremental costs (ΔC) to incremental health benefits (ΔH) between two alternatives ($\frac{\Delta C}{\Delta H}$). The increased cost of a treatment strategy is considered relatively cost-effective if its ICER is less than the value of a cost-effectiveness threshold (λ) [149]. The treatment strategy produces more health benefits, but less cost is the dominant strategy.

Also, the decision rules can be converted to the incremental net benefit (NB) under a certain cost-effectiveness threshold. The NB can further be described as the incremental

net monetary benefit (INMB) or the incremental net health benefit (INHB) [150] (calculation of net monetary or health benefits following equations in Table 2.7).

The relative cost-effectiveness of decision rules can be presented equivalently by the incremental net benefit of health or cost [151]. If the incremental net benefit of health or cost is greater than 0, then the treatment strategy or health technology is relatively cost-effective [149]. The cost-effectiveness threshold is the maximum cost required for decision-makers to pay for an additional unit of health outcome [152]. Although the actual value of the cost-effectiveness threshold in the NHS is uncertain, in general, the NICE guidance assumes the cost-effectiveness threshold falls within a plausible range between £20,000 and £30,000 per QALY gained in routine practice [133].

2.2.5 Decision-making under uncertainty

Uncertainty is inherent in any decision for relative cost-effectiveness and is a crucial influence on the decision-making process at the NICE guidance [133, 153]. Decision uncertainty is an incorrect decision made under specific probabilities not to give a relatively cost-effective recommendation [153]. The recommendation that is not relatively cost-effective will lead to an inefficient allocation of healthcare resources and result in health loss [153]. In general, three types of uncertainty are inherent in model-based economic evaluation [154].

Table 2.8. Types of uncertainty in decision-analytical models

Type of uncertainty	Definition
Methodological uncertainty	Uncertainty in the methods of conducting an economic evaluation
Structural uncertainty	Uncertainty in the conceptual and mathematical representation of a decision problem
Parameter uncertainty	Uncertainty in the values of a model's input parameters

(Source) Stevenson et al. (2014, p.62) [154]

Methodological uncertainty can be diminished by undertaking the appropriate economic evaluation method referred to in the NICE reference case [145]. Structural uncertainty can be diminished through thoroughly conceptualising the decision problem and modelling [154]. Since the true values of input parameters may not probably be accurate with certainty due to the data from a population level, deterministic sensitivity analysis methods can be used to evaluate the influence of outcomes by manually adjusting the values of one or more input parameters [155]. The NICE reference case suggested that probabilistic sensitivity analysis (PSA) should be used to characterise the joint uncertainty of all input parameters to ensure model appropriateness [133].

PSA demonstrates the parameter uncertainty introduced by input parameter estimates in model-based economic evaluation [156]. PSA characterise the input parameters in a decision-analytical model as probability distributions to represent the uncertainty in the true values instead of changing the values of one or more parameters as a point or range [157, 158]. Table 2.9 summarises some standard parameters used in decision-analytical models, logical constraints, data form, estimation methods and candidate distributions [142].

Table 2.9. Common parameters and candidate distributions

Parameters	Logical constraints	Form of data	Methods of estimation	Candidate distributions
Probability	$0 \leq \theta \leq 1$	Binomial	Proportion	Beta
		Multinomial	Proportions	Dirichlet
		Time to event	Survival analysis	Lognormal
Relative risk	$\theta > 0$	Binomial	Ratio of proportions	Lognormal
Cost	$\theta \geq 0$	Weighted sums of resource use	Mean, standard error	Gamma
				Lognormal
Utility decrements	$\theta \geq 0$	Continuous	Mean, standard error	Gamma
				Lognormal

(Source) Briggs *et al.* (2006), p 108 [142].

Monte Carlo simulation (random sampling) is adopted to give a value to the sample. The values of all input parameters for the sample are randomly generated following their respective distribution. Then the expected outcomes of interest (costs, QALYs, and net benefits) for each comparator strategy are estimated for the model. The simulation process is repeated many times to generate a distribution of outcomes, representing the joint uncertainty of the model's parameters [153, 155, 159]. Three types of intuitive graphical methods can scatter the uncertainty based on the PSA outputs: cost-effectiveness plane (CE plane), cost-effectiveness acceptability curves (CEACs) *etc*. [160-164].

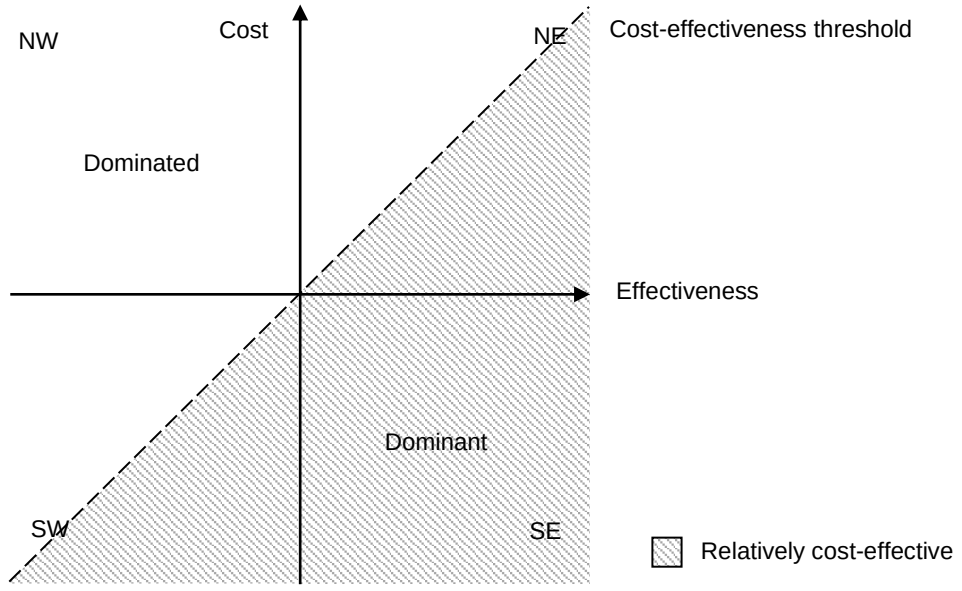
The cost-effectiveness plane (CE plane) illustrates the relative cost-effectiveness of alternative health technology strategies in a framework with two axes (abscissa is values of effectiveness (i.e., QALY); ordinate is cost values) (Figure 2.1) [1, 2].

Four quadrants (abscissa, ordinate) of the plane represent positive (+) or negative (-) values of cost and effectiveness, that is, northwest (NW: -, +), northeast (NE: +, +), southwest (SW: -, -) and southeast (SE: +, -) [1] (Figure 2.1). If the cost-effectiveness

result of the alternative strategy locates in the NW quadrant (called a dominated strategy), it produces less health at a higher cost than a different alternative. By contrast, if the cost-effectiveness result of the alternative strategy locates in the SN quadrant (also called a dominant strategy), which means it produces more health at a lower cost compared to a different alternative [3] (Figure 2.1).

The cost-effective threshold will decide whether the result is cost-effective if the result locates in SW or NE when health gains at a cost less than the cost-effectiveness threshold. When health is gained at the cost below the cost-effectiveness threshold (NE), or health is forgone at the cost upper the cost-effectiveness threshold (SW), the strategy is relatively cost-effective (Figure 2.1).

Figure 2.1. Illustration of cost-effectiveness plan



(Note) NW northwest; NE northeast; SW southwest; SE southeast.

CEAE plots the probability that each alternative strategy is relatively cost-effective over a range of cost-effective thresholds. The cost-effectiveness probability for an alternative strategy at a certain cost-effectiveness threshold is equal to the proportion of Monte

Carlo simulations in the PSA, where its net benefit is the largest. Therefore, the sum of the probability of cost-effectiveness for all alternatives must be one.

It is potentially beneficial for future research to conduct a subsequent model-based economic evaluation to reduce uncertainty. Resources may be used in the healthcare system to generate health gains or fund alternative research projects.

Value of information (VOI) analysis should be conducted to inform the necessity of further research based on PSA outputs [85, 165-167]. VOI analysis has been applied in the decision-making process and in prioritising the research decisions by the NHS Health Technology Assessment programme [86, 165, 168, 169]. VOI comprises three methods: (1) the expected value of perfect information (EVPI); (2) the expected value of perfect partial information (EVPPI); (3) the expected net benefit of sampling (ENBS).

There are, in general, three methods, by their complexity, that can inform growingly specific decisions for future research. The EVPI, as the most commonly used method, can estimate the overall potential value of further research to reduce decision uncertainty; the EVPPI can be used to estimate one or more specific parameters with the greatest value for future research; ENBS can be used to estimate the expected net benefit derived from specific research designs [170]. Population EVPI can be used to estimate the beneficiary population from alternative intervention and has been included in all published VOI examples [171-173], which were used in the thesis to provide the values for future research at a population level (Chapters 5 and 7).

In the decision and VOI analyses, the implicit assumption is that the health technologies have been implemented automatically into clinical practice. Nonetheless, the patients or clinical professionals may not adhere to decision-maker guidelines due to the complex conditions in routine clinical practice [174-177]. The non-adherence to relatively cost-

effective technologies compromises the efficiency of healthcare provision, and resources are forgone. For example, in this literature review, a proportion of patients eligible for surgery received PET instead, according to the national audit for breast cancer [11]. Adopting treatment strategies that are not cost-effective compromises the efficiency of healthcare provision in terms of health, and resources are forgone. For healthcare systems with budget constraints, implementing a relatively cost-effective decision should be promoted alongside healthcare provision and research funding decisions. The analytical framework developed by Fenwick *et al.* (2008) [178] was used in this PhD study to estimate the value of implementation based on the level of implementation (current or perfect). The EVPIM is the difference between the expected value of a decision that is implemented perfectly and the current level [178].

2.3 Conclusion

Although PET was recommended for patients with strong ER+ and shorter life expectancy (e.g., frail or comorbid patients), PET has been widely used as an alternative strategy to surgery in older women based on four main hypotheses:

1. Tumour biological characteristics, i.e., ER positivity in older patients, are higher than in younger counterparts. ET is a recommended adjuvant treatment strategy or primary treatment strategy for ER+ women with breast cancer;
2. Physical functioning as a key indicator is determined by which treatment can be received, i.e., surgery or PET. In general, the older population had inferior physical functioning to their younger counterparts;
3. Patient preference is another factor in determining which treatment is received for older patients. Older patients are more likely to receive a treatment that is less intensive or has less influence on their quality of life;
4. Current clinical evidence of a systematic review of RCTs indicated no difference in overall survival between surgery and PET in older patients who are fit for surgery.

However, robust economic evidence is lacking to support the cost-effectiveness of PET versus surgery in older patients. This lack of evidence would compromise the efficiency of healthcare resource allocation and reduce the probability of selecting optimal treatment with maximised clinical and cost-effectiveness by clinicians and patients. This thesis will develop a series study to evaluate the clinical and cost-effectiveness of older women with early-stage breast cancer at various levels of physical functioning in England to improve the healthcare system efficiency of resource allocation and healthcare service quality.

2.4 Research questions

In summary, based on the current evidence for older women with ER+ early-stage breast cancer summarised in Chapter 2, a general research question was proposed: What is the effective and cost-effective treatment strategy (i.e., surgery versus PET) in treating older women with ER+ early-stage breast cancer and impaired physical functioning?

To achieve this goal, there are five sub-research questions included:

1. What model structure and evidence source are used to estimate input parameters for the model-based economic evaluation? (Chapter 3)
2. Are any studies measuring the health state utility for older women with early-stage breast cancer? What is the decrement value of health state utility with age increasing for older women with early-stage breast cancer? (Chapter 4)
3. What is the cost-effective strategy of PET versus surgery in older women who are physically fit for surgery? How many health forgone when a strategy is used that is not cost-effective under the nonadherent routine clinical practice? (Chapter 5)
4. What is the clinical and comparative effectiveness of PET and surgery in older women with ER+ early-stage breast cancer by levels of frailty and comorbidity? (Chapter 6)

5. What is the cost-effective strategy of PET versus surgery in older women unfit for surgery (i.e., by levels of frailty)? How valuable is it to fund more research for older women with ER+ early-stage breast cancer receiving surgery or PET in future? (Chapter 7)

Chapter 3 The evidence sources applied to cost-effectiveness analyses for older women with early-stage breast cancer

Chapter 3 investigates the full-economic evaluation of older women aged ≥ 70 years with early-stage breast cancer. The chapter is presented as a standalone study in terms of an introduction (Section 3.1), aim and objectives (Section 3.2), methods (Section 3.3), results (Section 3.4), discussion (Section 3.5), and conclusion (Section 3.6). The published manuscript of this chapter is included in Appendix 3.

3.1 Introduction

Decision-analytic models are essential to produce cost-effectiveness evidence by synthesising all relevant evidence and extrapolating expected cost and health outcomes over a lifetime (Chapter 2). Markov model was the most commonly used model structure in previous economic evaluations, as minimum typical three health states of the Markov model structure such as 'disease-free', 'recurrence' (or 'progressed disease'), and 'dead' have been used for conceptualising the decision problem of breast cancer (Chapter 2) [179]. This structural characterisation of disease is unlikely to vary by the age of diagnosis.

RCTs or systematic reviews of RCTs (Chapter 2) are the commonly used evidence sources for estimating input parameters to populate the decision-analytical models. Most randomised controlled trials (RCTs) of treatments for breast cancer, for example, have excluded older patients due to their higher risk of morbidity and mortality or have recruited relatively low numbers of older patients [180]. Therefore, in the absence of data from older patients to populate fundamental input parameter values, indirect evidence sources from younger patients may be used to help estimate the cost-effectiveness of treatment strategies for primary breast cancer in an older population.

Potential challenges may arise by using indirect evidence from younger patients if there are systematic differences with older patients in, for example, resource use, health-related quality of life (HRQoL), the natural history of the disease, or treatment benefits and harms. Older patients with breast cancer may interact more with the healthcare system and consume greater quantities of healthcare resources post-treatment than younger patients because of their higher likelihood of comorbidity and frailty. Similarly, age-related comorbidities may result in older patients having relatively lower health-state utility values than younger patients [181]. The natural history of the disease may vary between younger and older patients if prognostic factors (such as endocrine receptor positivity) differ across age groups [182]. The magnitude and duration of benefit or direct harm from treatment (for example, the severity of adverse events after receiving chemotherapy) will likely depend on frailty experienced to a greater extent by older patients than younger patients [183].

In light of these potential differences between older and younger patients with primary breast cancer, if data from younger patients are used to populate input parameter values to estimate the expected cost and health outcomes of treatment strategies for older patients, analysts and decision-makers will need to appraise whether these sources of evidence are appropriate for the target population of the economic evaluation [184]. Inappropriate input parameter values may result in inaccurate cost-effectiveness estimates, decision uncertainty, and the value of undertaking further research for older patients. The results from Chapter 3 informed the model structure and identified potentially appropriate evidence sources to estimate the input parameters used in the economic evaluations (Chapters 5 and 7).

According to the NICE guidance, current economic evidence should be synthesised before investigating the cost-effectiveness of a specific treatment [83]. As there is a lack

of economic evidence to indicate the cost-effectiveness of PET versus surgery in older women with early-stage breast cancer, a systematic review was conducted to critically appraise evidence sources used to estimate input parameters in model-based economic evaluation to develop a cost-effectiveness analysis in comparing PET against surgery for older women with early-stage breast cancer.

3.2 Aim and objectives

Chapter 3 aimed to appraise the sources of evidence and methods to estimate input parameter values in decision-analytic model-based cost-effectiveness analysis of treatments for primary breast cancer in older patients (≥ 70 years old). Two objectives included to meet the aim:

(1) To identify all published model-based economic evaluations for older women with early-stage breast cancer;
(2) To critically appraise all published model-based economic evaluations for older women with early-stage breast cancer.

3.3 Methods

This study reports a systematic review of all published economic evaluations of treatments (including surgery and any adjuvant or non-adjuvant treatments) for older females (≥ 70 years old) with early-stage primary breast cancer following the principles of the Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Systematic Reviews (PRISMA) guidance [185] (Appendix 4).

This review focused on the methods used by the included economic evaluations to estimate four types of input parameters: (i) health-related quality of life (HRQoL), (ii) the natural history of the disease, (iii) the magnitude of relative treatment effects, and (iv) resource use. First, these four elements are critical information to estimate the input

parameters for the modelling, including transition probabilities between states (estimated by the natural history of the disease and the magnitude of relative treatment effects), QALYs for each health state (estimated by HRQoL), and cost for each state and treatment (estimated by resource use). Meanwhile, if the study population of the evidence source used to estimate the input parameters is inconsistent with the target population for the economic evaluation, whether there are methods that can be used to adjust for the target population.

3.3.1 Eligibility criteria

The criteria for inclusion and exclusion in the systematic review were based on the PICO framework [186], i.e., Population (older women aged 70 years or more with early-stage primary breast cancer), Intervention (any treatment, including surgery with or without adjuvant therapy), Comparator (any therapy), Outcome (incremental cost and health outcomes), and Study design (full economic evaluation) (Table 3.1). A full economic evaluation is defined as "*the comparative analysis of alternative courses of action in terms of both their costs and consequences*" [187], including cost-effectiveness analyses (CEA), cost-utility analyses (CUA) and cost-benefit analyses (CBA) that use a decision-analytic model. Conference abstracts and manuscripts written in a non-English language were excluded.

Table 3.1 Systematic review inclusion and exclusion criteria

Concepts	Inclusion criteria	Exclusion criteria
Population and conditions	Older women aged 70 years or more with (operable, Stage I, Stage II, or early) breast cancer	• Only the aged below 70 years • Only premenopausal women • Only male breast cancer • Only metastatic breast cancer • Only locally advanced breast cancer • Only recurrence of breast cancer • Unconfirmed breast cancer • Only non-invasive breast cancer • Other diseases
Intervention	Surgery with/without adjuvant therapy	• Head-to-head comparison • Test to determine response after treatment • Procedures for diagnosis of breast cancer • Preventive strategy • Preoperative therapy • Nursing or rehabilitation care
Comparison	Any treatments	• Treatments or prevention for adverse drug events • Treating of cancer complications • Follow up strategy
Outcome	Any outcome	• Non-economic evaluation outcome, for example, treatment preference or quality of life
Study Design	Full economic evaluation (CUA, CEA, CUA) that used a decision-analytic model in a peer-reviewed publication	• Partial economic studies (cost of illness study, outcome description, cost description, outcome and cost descriptions, cost analysis) • Systematic review • Clinical trials, observational studies
Language	English	• Other languages without English translation
Publication	Full-text article	• Conference abstract or proceeding abstracts without full article • Letter to editors, editorial, commentary, and news

3.3.2 Information sources and search strategy

Ovid EMBASE® (1974 to 2021 Week 35) and Ovid Medline® (1964 to September 2021) were searched electronically from inception until September 2021. The search strategy (Appendix 5) comprised disease-specific terms for early-stage primary breast cancer and terms to identify published economic evaluations according to the filters reported by the Centre for Reviews and Dissemination [188].

3.3.3 Study selection and data collection

The titles and abstracts identified by the search strategy were screened independently for relevance against the inclusion criteria by two investigators (YW and LCC). The full texts of eligible studies were further retrieved and reviewed independently by two investigators (YW and LCC) to finalise study selection. At the full-text review stage, the age of the target population for the base-case analysis and, if relevant, for any age-specific subgroup analyses was identified within each economic evaluation to determine whether the study was designed for patients at least 70 years old. Discrepancies were resolved through consultation with a third reviewer (SG) to make a final decision.

3.3.4 Data items

Data extraction comprised two stages. In the first stage, the following data were extracted from each economic evaluation by one author (YW): (1) study design (country; target population; strategies compared), (2) study characteristics (evaluation method, i.e., CEA or CUA; type of decision-analytic model; time horizon; perspective; health outcome measure used, and costs included), (3) references of the evidence sources that were used to estimate four types of input parameter values (HRQoL; the natural history of the disease; relative treatment effect; and resource use/cost), (4) methods of analysis (whether deterministic/probabilistic sensitivity analyses or value of information (VOI) analyses were reported), and (5) estimated results (base-case and sensitivity analyses,

VOI, and key drivers of relative cost-effectiveness through sensitivity analysis). In the second stage of data extraction, the characteristics of the estimation sample (sample size and mean age) were extracted from the original sources of evidence used by the included economic evaluations to estimate their input parameter values. Four selected input parameters were extracted and appraised due to the suggestion by Zechmeister-Koss et al. (2014) [146] (Details in Section 2.2.3 Table 2.6).

3.3.5 Quality assessment

The completeness of reporting in each economic evaluation was assessed by 17 items in the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [189]. Full adherence to any item was noted as 'Yes', partial adherence was indicated as 'Partial', and non-adherence as 'No'. Two researchers (YW and LCC) independently appraised each identified economic evaluation's quality. Any discrepancies were discussed with a third reviewer (SG) to make a final decision. Quality assessment was summarised visually and reported by a narrative synthesis.

3.3.6 Data synthesis

The extracted data from each economic evaluation were first reported in a table and summarised by a narrative synthesis. This summary described the sample of included economic evaluations according to the type of decision-analytic model used, the proportion of studies with a target population of patients at least 70 years old in either the base-case or subgroup analysis, the treatment strategies compared, and the main results of each economic evaluation.

For each economic evaluation, the sources of evidence used to estimate four types of input parameters were then appraised to determine whether they were obtained from an

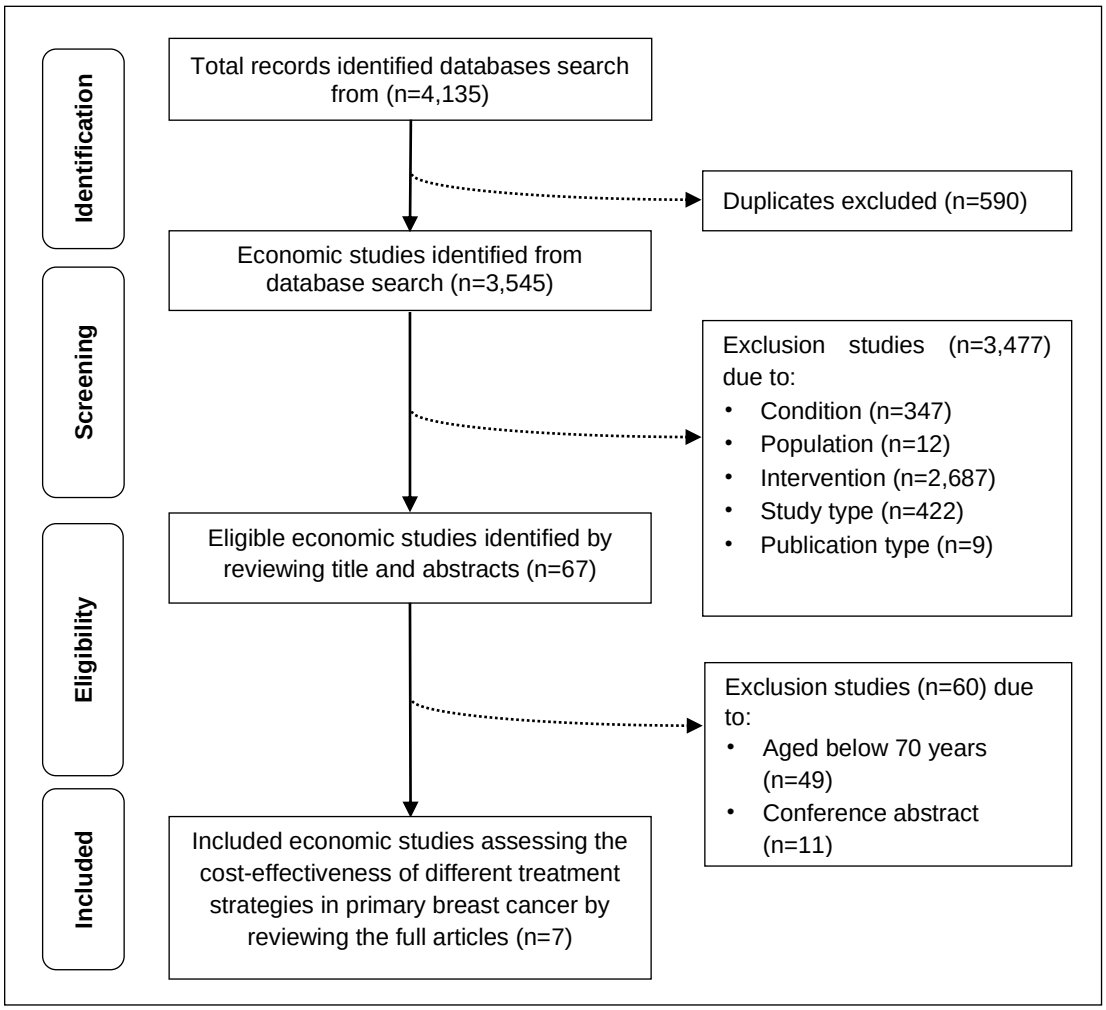
estimation sample that corresponded with the age of the target population (i.e., ≥ 70 years old). For the remainder of this study, (1) 'HRQoL' refers to the health state utility values, (2) the 'natural history of disease' refers to the probability of health events in the absence of a treatment effect, (3) the 'relative treatment effect' refers to the magnitude of difference between two treatments, and (4) 'resource use' refers to the direct health care resources consumed by patients.

In the cases where evidence for input parameter values was based on an estimation sample of patients younger than 70 years old, the methods of each economic evaluation were then appraised to determine whether any adjustment or calibration was performed to make these estimated values more appropriate for an older population. Calibration or adjustment has been seen as adjusting to ‘unobserved’ or unavailable parameter values to achieve a good fit with the data [190]. Since there is a lack of evidence source of older women with early-stage breast cancer receiving PET, approaches have been used to adjust the input parameters estimated from the study for their younger counterparts to fit the older patients.

3.4 Results

The PRISMA diagram illustrates the identification, screening and inclusion of studies. The electronic database searches identified 3,544 studies, and 67 were read in full. The final sample comprised seven decision-analytic model-based economic evaluations of treatments for primary breast cancer in patients aged 70 years or more [191-197] (Figure 3.1).

Figure 3.1. Selection of economic evaluations into this review



3.4.1 Characteristics of included studies

All the included economic evaluations reported both CEA and CUA. The decision-analytic models used by the identified economic evaluations included a cohort Markov model (n=3) [193, 194, 197] and a patient-level simulation (n=2) [195, 196]. Two studies [191, 192] did not report the type of decision-analytic model. All eight economic evaluations used at least three health states within the structure of their decision-analytic model (disease-free, progressed disease, and dead). Different clinical outcomes were used between the economic evaluations to define the health state for progressed disease, including recurrence, local relapse, or metastasis. The structure of the decision-analytic

model in four studies [194-197] also included an additional health state for treatment side effects. (Table 3.2, Full data extraction in Appendix 6)

Four economic evaluations (43%) had a base-case target population that focused exclusively on older patients aged ≥ 70 years [193, 195, 196]. The two studies by Ward *et al.* [195, 196] had a base-case target population of patients aged 70 years or older with ER+ invasive breast cancer. Sen *et al.* [193] reported results for 70, 75 and 85 years old with early-stage breast cancer.

Four economic evaluations (57%) reported cost-effectiveness estimates for older patients as part of subgroup analysis by age [191, 194, 197]. The two studies by Naeim *et al.* reported results for subgroups of patients aged 75 and 85 who had early-stage node-positive [191] and node-negative [191] breast cancer. Desch *et al.* [197] reported results for a subgroup of patients aged 60 to 80 years old with a diagnosis of primary breast cancer, and Skedgel *et al.* [194] reported results for subgroups of patients aged 70 years and ≥ 80 years old.

Three studies [193, 194, 197] compared surgery alone with either adjuvant chemotherapy alone [197], radiotherapy [193], or chemotherapy ± trastuzumab [194]. These three studies indicated that surgery alone was more cost-effective than surgery plus adjuvant treatments for the older population [193, 194, 197] (Table 3.2). Two studies compared surgery plus adjuvant chemotherapy with adjuvant chemotherapy ± endocrine therapy [191]. Two studies compared surgery plus adjuvant radiotherapy with adjuvant endocrine therapy and their combination [195, 196]. Of these four studies, which compared different adjuvant strategies, the estimated results suggested that less adjuvant treatment, or less harmful adjuvant treatment (i.e., less intensive radiotherapy or less toxic chemotherapy), was more cost-effective for older patients with breast cancer [191, 192, 195, 196]. No published economic evaluation compared surgery with non-

surgical treatment as the initial strategy to manage older patients with primary breast cancer (Table 3.2). In addition, no identified economic evaluation reported a value of information (VOI) analysis to investigate the need for further research to reduce uncertainty in the estimates of relative cost-effectiveness [198] (Table 3.2).

Table 3.2. Summary of characteristics for included studies

Study, country	Target population	Type of model	Perspective, type of study	Intervention and Comparator	Results
Surgery plus adjuvant treatments used for comparisons					
Naeim and Keeler [191] USA	**Subgroup analyses:** 45,65, 75, 85 years women with early-stage node (+) breast cancer	Not stated	Health care provider CUA and CEA	(i) Adjuvant chemo alone (CMF) (ii) Adjuvant chemo alone (AC) (iii) Adjuvant endocrine alone (Tamoxifen) (iv) Adjuvant Chemo (CMF) + Tamoxifen (v) Adjuvant Chemo (AC) + Tamoxifen	Adjuvant endocrine treatment was cost-effective in older women.
USA	**Subgroup analyses:** 45,65, 75, 85 years women with early-stage node (+) breast cancer	Not stated	Health care provider CUA and CEA	(i) Adjuvant chemo alone (CMF) (ii) Adjuvant chemo alone (AC) (iii) Adjuvant endocrine alone (Tamoxifen) (iv) Adjuvant Chemo (CMF) + Tamoxifen (v) Adjuvant Chemo (AC) + Tamoxifen	Adjuvant endocrine treatment was cost-effective in older women.
War *et al.* (2019) [196] USA	**Older women targeted:** 70 years or older with estrogen-positive invasive breast cancer	Patient-level Markov microsimulation	Societal CUA and CEA	(i) Adjuvant radiotherapy (Aromatase inhibitor alone) (ii) Adjuvant endocrine (APBI-alone)	Adjuvant endocrine treatment was the dominant strategy
Ward, Vicini [195] USA	**Older women targeted:** 70 years or older with estrogen-positive invasive breast cancer	Patient-level Markov microsimulation	Societal CUA and CEA	(i) Adjuvant endocrine (Aromatase inhibitor alone) (ii) Adjuvant radiotherapy (APBI-alone) (iii) their combination	Adjuvant endocrine treatment was the dominant strategy

Study, country	Target population	Type of model	Perspective, type of study	Intervention and Comparator	Results
Surgery adopted as baseline intervention					
Desch, Hillner [197] USA	**Subgroup analyses:** 60 to 80 years women with a diagnosis of primary breast cancer	Markov model	Societal CUA and CEA	(i) Surgery alone (ii) Adjuvant chemotherapy alone	Adjuvant chemotherapy was cost-effective for younger women
Skedgel, Rayson [194] Canada	**Subgroup analyses:** 40, 50, 60, 70 and 80+ years of women with T1bN0 breast cancer	Markov model	Direct payer CUA and CEA	(i) Surgery alone (ii) Adjuvant chemotherapy alone (iii) Adjuvant chemotherapy + concurrent trastuzumab (iv) Adjuvant chemotherapy + sequential trastuzumab	Additional trastuzumab treatment gave limited benefits
Sen, Wang [193] USA	**Older women targeted:** 70, 75, and 80 years women with early-stage breast cancer	Markov model	Payer CUA and CEA	(i) Surgery alone (ii) Adjuvant Radiotherapy EBRT (iii) Adjuvant Radiotherapy IMRT	EBRT was the dominant strategy

(Note) CEA: cost-effectiveness analysis; CEA: Cost-effectiveness analysis; CUA: cost-utility analysis; AC: adriamycin and cyclophosphamide; CMF: cyclophosphamide, methotrexate and 5-fluorouracil; EBRT: External beam radiation therapy; IMRT: Intensity-modulated radiotherapy; APBI: accelerated partial-breast irradiation.

3.4.2 Quality assessment

Table 3 reports the quality assessment of the seven economic evaluations according to the CHEERS criteria (Table 3.3). The included studies reported thirteen domains of the CHEERS criteria (76%). However, in general, the economic evaluations whose base-case target population comprised older patients exclusively reported the sources of evidence to estimate input parameters more clearly than the economic evaluations that reported results for older patients as part of a subgroup analysis (Table 3.3). Seven economic evaluations reported analytical methods in detail and partially reported study parameters which justify the critical appraisal of these values for the remainder of this review.

Table 3.3. Reporting of each economic evaluation according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) criteria

Study	CHEERS criteria																
	Target population and subgroups	Setting and location	Study perspective	Comparators	Time horizon	Discount rate	Choice of health outcomes	Measurement of effectiveness	Measurement and valuation of preference-based outcomes	Estimating resources and costs	Currency, price date, and conversion	Choice of model	Assumptions	Analytical methods	Study parameters	Characterising uncertainty	Characterising heterogeneity
Naeim *et al.* (2005) [191]																	
Naeim *et al.* (2005) [192]																	
Skedgel *et al.* (2013) [194]																	
Sen *et al.* (2014) [193]																	
War *et al.* (2019) [196]																	
Ward *et al.* (2020) [195]																	
Desch *et al*. (1993) [197]																	

(Note) Key: has the item been reported?

Yes Partial No

3.4.3 Analysis of Evidence Sources for Input Parameters

The economic evaluations' sources of evidence and methods to estimate four types of input parameters (HRQoL, natural history, treatment effect, and resource use) are presented as follows. The selected parameters (Details of the above four input parameters and related evidence source in Supplementary Appendix 7)

3.4.3.1 Health-related quality of life

All eight economic evaluations reported expected health outcomes as quality-adjusted life years (QALYs). The EQ-5D instrument was used to estimate HRQoL in four studies [194-196, 199]. Three studies estimated HRQoL values by expert elicitation [191, 197]. Across the included economic evaluations, four approaches were taken to make the HRQoL values a function of the target population's age: (1) HRQoL, which was independent of age; (2) partial age-dependent HRQoL; (3) age-dependent HRQoL with a disutility multiplier; and (4) age-dependent HRQoL with an additive utility decrement (Table 3.4).

Table 3.4. Sources of evidence to estimate the health-related quality of life

Author, year	Health state	Instrument and data source	Target population	Sample size, mean age	Method of age adjustment
Without the adjustment of age					
Naiem et al [191, 192]	**Disease-free** Baseline **Progression**: hormone therapy minor toxicity with chemotherapy major toxicity with chemotherapy	Not reported Expert elicitation [200, 201]	45 years 65 years 75 years 85 years	150 Not reported	No
Desch, Hillner [197]	**Disease-free** Well **Progression**: First recurrence **Side effect** Minor toxicity with chemotherapy Major toxicity with chemotherapy	Not reported Assumptions	60 years 65 years 70 years 75 years 80 years	NA	NA
With the adjustment of age					
Skedgel, Rayson [194]	**Disease-free**: Disease-free baseline varied by age **Progression**: First local recurrence Second local recurrence Well after relapse Distant recurrence **Side effect** Congestive heart failure Febrile neutropenia AML/MDS Nausea/vomiting	EQ-5D-3L from previous literature [202] for baseline value Utilities for side effects: from the Cost-Effectiveness Analysis Registry without reporting data source	40 years 50 years 60 years 70 years 80+ years	2981, 74 years [202] Not reported for side effects	Partial adjustment: Age-dependent baseline values and fixed progression state values

Author, year	Health state	Instrument and data source	Target population	Sample size, mean age	Method of age adjustment
Sen, Wang [193]	**1. Health states** **Disease-free:** Surgery alone Surgery by different adjuvant treatments **Progression:** Recurrence Distant metastasis **2. Utility modifier** 70–74 y 75–79 y 80–84 y >85 y	1. EQ-5D from previous literature [203] 2. Standard Gambles from previous literature [204]	70, 75, and 80+ years	Not reported	Age-dependent baseline values and health-state utilities by multiplying the standard gamble utilities by the mean age-specific utility

Author, year	Health state	Instrument and data source	Target population	Sample size, mean age	Method of age adjustment
Ward *et al.* (2019) [196] Ward *et al.* (2020) [196]	**1. Utility** **Disease-free** Baseline **2. Disutility value:** **Progression** Distant metastasis Second malignancy: radiation Induced salvage mastectomy salvage axillary dissection after axillary recurrence **Side effect** Fracture Second malignancy: endometrial cancer salvage lumpectomy with radiation treatment of contralateral cancer Cardiac adverse event (MI) DVT Acute radiation dermatitis, Grade 3 Hot flashes Arthralgia Late radiation-induced fibrosis	1. Utility EQ-5D from a cross-sectional U.S. population survey 2005 [205] 2. Disutility from previous economic evaluation [206]	70 years or older	965 patients of a sub-cohort aged 65-74 years [205]	Age-dependent baseline values and health-state utilities with an additive utility decrement

(Note) DVT: Deep vein thrombosis; AML/MDS, acute myeloid leukaemia and/or myelodysplastic syndrome; MI: myocardial infarction; * disutility used in the study

The two studies by Naiem [191, 192] used HRQoL values fixed across age subgroups and were independent of the target population's age. Patients were assumed to have lower utility if they received hormone therapy (HRQoL=0.99) or chemotherapy with minor toxicity (HRQoL=0.90), or major toxicity (HRQoL=0.8). Similarly, Desch [197] also assumed that patients had the same utility values after experiencing minor and major side effects from chemotherapy. This approach may overestimate the expected QALYs accrued by older patients if the loss of HRQoL due to treatment-related adverse events is greater than for younger patients.

Skedgel *et al.* [194] estimated HRQoL values, which were partially dependent on the age of the target population. The utility values for patients who were 'disease free' were calculated using EQ-5D data from the Medical Expenditure Panel Survey (MEPS) between 2000 and 2002 [202] (n=38,678 adults). This approach enabled the authors to account for the general population's negative association between age and HRQoL. However, the HRQoL values for subsequent health states (for example, recurrence, second recurrence) and adverse events (for example, nausea) appeared to be fixed and independent of age.

Sen *et al.* [193] used a disutility multiplier to estimate HRQoL values, which depended on the age of the target population. Sen *et al.* also used the MEPS (1998-99) to estimate age-dependent EQ-5D values for patients after successful treatment to preserve the negative association between age and HRQoL in the general population. Utility values for subsequent health states (for example, local recurrence) were estimated from a published standard gamble study with 97 patients [203]. The authors then adjusted these utility values using a disutility multiplier based on the mean age-dependent EQ-5D values from the MEPS. Disutility is the decrement in utility values because of specific conditions or characteristics (for example, ageing) [207].

A disutility multiplier is an approach using disutility to adjust the health state utility values due to specific characteristics (for example, different treatment, age increase, or frailer conditions). This approach ensured that, on average, the HRQoL values accrued by patients who experienced these subsequent health states reflected the observed decline of HRQoL over their lifetimes. For example, the estimated HRQoL value for local recurrence was lower for older than younger patients.

Ward *et al*. [195, 196] used an additive utility decrement to estimate HRQoL values, which depended on the patient's age. A representative cross-sectional survey of the US population (n=4,000) estimated a baseline EQ-5D value for 70-year-old females between 2005-06 [205]. Most subsequent health states had a corresponding disutility subtracted from this baseline EQ-5D value as an additive decrement (i.e., baseline HRQoL – disutility = new HRQoL). Like Sen *et al.*, this approach enabled the authors to estimate HRQoL values for patients who entered subsequent health states, accounting for the lower HRQoL experienced by older patients, on average, compared with younger patients.

3.4.3.2 Natural history of the disease

The included economic evaluations used four methods to estimate input parameters that reflected the natural history of breast cancer: (1) data were used from younger patients without adjustment; (2) data were used from older patients without adjustment; (3) plausible values were assumed and varied in a sensitivity analysis, and (4) data were used from younger patients and calibrated for an older population (Table 3.5).

The two economic evaluations by Naiem *et al.* [191, 192] estimated the 10-year breast cancer-specific mortality for patients aged 75 and 85 from studies where the estimation sample was younger (for example, between 50-55% of the sample was below 55 years old). This approach may have underestimated the probability of death in the target

population if the 10-year breast cancer-specific mortality is higher for older patients than younger patients. In contrast, Sen *et al.* [193] estimated the probability that patients experience health states (for example, recurrence and metastasis) from published data of a trial that had recruited a sample of older females with breast cancer. The probabilities derived from these trial data were likely more representative of an older population, given that the target population of Sen *et al.*'s economic evaluation and the estimation sample of the trial had similar patient characteristics.

Skedgel *et al.* argued that their target population's prior probability of recurrence was unknown. To handle this, the authors assumed a range of plausible values for the probability of recurrence across different ages. One advantage of this approach was that the impact of varying the probability of recurrence on cost-effectiveness estimates could be explored in a sensitivity analysis. Ward *et al.* [195, 196] estimated transition probabilities using data from a published trial whose sample was younger than 70 years old. To make these data more representative of an older population, the authors used calibration methods by applying a 'reduction factor' to the annual event rate in both arms of the trial. This approach reduced the absolute risk of events and made the input parameter values more appropriate for an older population.

Table 3.5. Sources of evidence to estimate the natural history of the disease

Author, year	Parameters used in studies	Data source	Age of target population	Mean age of estimation sample
From previous economic evaluations				
Skedgel, Rayson [194]	**Disease-free to recurrence** Proportion local recurrence/recurrence 'Instant' conversion from local to distant **Side effects** Rate of nausea |vomiting (grades 3 + 4) Rate of febrile neutropenia Rate of CHF Relative mortality risk |CHF Rate of AML/MDS Relative mortality rate |AML/MDS Relative risk of cardiotoxicity | conTZ Relative risk of cardiotoxicity | seqTZ	Recurrences from previous economic evaluations [208-210]. Adverse side-effects from previous trials [211, 212]	40 years 50 years 60 years 70 years 80+ years	Patients aged >70 years account for 16% [212] Patients aged >60 years account for 16.3% [211]
From randomised controlled trials				
Naiem et al [191, 192]	**Odds reduction of 10-year mortality** **Disease-free to death** Adjuvant Chemo CMF Adjuvant Chemo AC Adjuvant Tamoxifen Adjuvant Chemo CMF + Tamoxifen Adjuvant Chemo AC + Tamoxifen	Background non-cancer mortality from United States life tables 1997 [213];	45 years 65 years 75 years 85 years	Age-specific mortality from 0 to 100 years
Sen, Wang [193]	**Disease-free to recurrence no RT** **Disease-free to recurrence + RT** **Recurrence to metastasis** **Metastasis to death**	Clinical trial [214]	70, 75, and 80 years	> 70years
Ward, Vicini [195] and War *et al.* (2019) [196]	**Cumulative incidence** **Disease-free to death** Overall survival Death from 2nd cancer **Disease-free to progression**	Clinical trials[196, 214-218]	70 years or older	70years [214] >65 years [215] 65.7 years [216] 57 years [217] Not reported [218]

Author, year	Parameters used in studies	Data source	Age of target population	Mean age of estimation sample
	Ipsilateral breast tumours recurrence Contralateral breast cancer Distant metastasis **Side effects** Osteopenia requiring bisphosphonate Bone fracture Deep vein thrombosis Fibrosis/soft-tissue necrosis Hot flashes Arthralgia Radiation dermatitis, acute grade 3			
Desch, Hillner [197]	**Disease-free to progression** First recurrence Relative reduction in breast cancer recurrence with chemotherapy	Clinical trials [219, 220]	60 years 65 years 70 years 75 years 80 years	48 years [219] Not reported [220]

(Note) seqTZ, Sequential trastuzumab; conTZ, concurrent trastuzumab; AML/MDS, acute myeloid leukaemia and/or myelodysplastic syndrome; CHF, chemotherapy-related congestive heart failure; AI: Aromatase inhibitor; Accelerated partial-breast irradiation: APBI.

3.4.3.3 The magnitude of treatment effects

The economic evaluations used four methods to incorporate age-specific heterogeneity in the relative treatment effects. These methods include (1) direct estimation of age-specific treatment effects from RCT or meta-analysis data; (2) scenario analyses of plausible age-specific treatment effects in the absence of data; (3) the use of observational patient-level data to estimate age-specific treatment effects; and (4) the incorporation of age-specific behavioural parameters to modify the treatment effect.

Skedgel *et al.* [194] assumed that the relative treatment effect for adjuvant chemotherapy was a function of the patient's age. The author estimated hazard ratios for 'premenopausal' (40 and 50 years) and 'postmenopausal' (60 and 70 years) patients using RCT data [211, 212]. These data indicated, for example, that adjuvant chemotherapy was less effective at reducing recurrence for older patients (HR: 0.672) than younger patients (HR: 0.563). The authors then assumed that the relative treatment effect for adjuvant trastuzumab was the same for both older and younger patients. Similarly, Desch *et al.* [197] assumed that the annual relative reduction in recurrence for patients aged 60 to 69 years old was 20%, compared with 30% for younger patients, according to data from a meta-analysis of RCTs [219, 220].

Naiem *et al.* [191, 192] first estimated the relative treatment effect of adjuvant therapies (odds-reduction of 10-year mortality) from a meta-analysis of RCTs for patients aged 45 years and 65 years old. Without evidence for the relative treatment effect in 75-years and 85-years old patients, the authors assumed three possible values (low, medium, and high treatment effects). In the 'high' scenario, the magnitude of the treatment effect was assumed to be equivalent to that for a 65-year-old patient. The authors then estimated how reducing this treatment effect in older patients may impact cost-effectiveness estimates using the 'medium' and 'low' scenario analyses. The details to calculate the

medium values (extrapolated the trend of less benefit with increasing age) and the low values (minimal benefit) were not described explicitly.

Sen *et al.* [193] incorporated age-specific heterogeneity in the relative treatment effect by performing patient-level data analysis from the observational Surveillance, Epidemiology, and End Results (SEER) Program. The authors estimated radiotherapy's 5-year and 10-year overall survival compared with surgery. The estimated treatment effects were stratified by age groups (70-74, 75-79 and 80-89 years old).

Ward *et al.* [195, 196] incorporated a behavioural parameter to reflect evidence that adherence to endocrine therapy may reduce in older patients. Data from a registry study of patients at least 65 years old estimated that compliance with endocrine therapy was 61% at five years. In the economic evaluation, this reduction of adherence had a subsequent impact on the relative effectiveness of endocrine therapy. By including this behavioural parameter, the authors could model potential changes in treatment's relative effectiveness as patients age.

3.4.3.4 Resources and cost

The included economic evaluations used two methods to estimate input parameters for resource use: (1) estimated input parameters were independent of age, and (2) estimated input parameters were dependent on age (Table 3.6).

Five economic evaluations assumed that estimates of resource use were independent of each patient's age. Naeim and Keeler [191] estimated the resources used for managing the side effects of adjuvant chemotherapy (10% of patients needed treatment to manage low white cell counts, and 3% of patients required hospitalisation for neutropenic fever) based on data from an RCT that had a sample of younger patients

(81% of the sample was ≤ 49-years old) [221]. However, this approach may have underestimated the resources required if hospitalisation rates or treatment for low white cell counts are higher in an older population [222].

Skedgel *et al.* [194] extracted the local and distant recurrence costs from published costing studies [223]. These cost estimates were fixed for all age subgroups. The mean age of the sample in the published costing study was not reported, so it was unclear whether these data applied to a population of 70-year-old patients with primary breast cancer. Ward [195, 196] estimated direct and indirect costs using a hospital database and clinical guidelines. However, the authors did not report how the estimated cost of the metastatic disease ($23,460) was calculated.

Three economic evaluations estimated age-specific input parameter values for resource use [193, 197]. Desch *et al.* [197] extracted cost data from previously published economic evaluations [224, 225] and assumed that the total costs of breast cancer treatment decreased as patients got older. This assumption was based on reduced follow-up costs, fewer late recurrences, and increased mortality from other causes over time.

Sen *et al.* estimated age-specific (70-74, 75-79, and 80-94 years old at diagnosis) cancer-related costs by conducting a matched cohort study from the SEER-Medicare database. Cancer patients were matched with non-cancer patients based on age, race, comorbidity, region, and year of diagnosis. All costs (inpatient, outpatient, physician, home health, hospice, and Durable Medical Equipment claims) for cancer and non-cancer patients were estimated over the 2 months before and up to 12 months after, date of diagnosis, and then stratified by type of initial treatment received. The cancer-related

costs differed between the total cost accrued by cancer patients and their matched control [193].

Table 3.6. Sources of Evidence to Estimate Resource Use

Author, year	Inclusions	Data source	Age of target population	Mean age of estimation sample
Direct cost				
Naeim and Keeler [191] and Naeim and Keeler [191]	**Treatments** Adjuvant chemo alone (CMF) Adjuvant chemo alone (AC) Adjuvant endocrine alone (Tamoxifen) Adjuvant Chemo (CMF) + Tamoxifen Adjuvant Chemo (AC) + Tamoxifen	Published guidelines, research studies, and expert opinions of the treatment. Managing side effects of adjuvant chemotherapy from clinical trials [221]	45 years 65 years 75 years 85 years	Not reported
Skedgel, Rayson [194]	**Treatment** TC course FEC-D course 12 months adjuvant trastuzumab, per case **Health states** Local recurrence, per case Distant recurrence, per case Post-recurrence follow-up per month **Side effect** Febrile neutropenia, per case AML/MDS, per month Chemo-related CHF, per month Chemo-related nausea and vomiting, per case Trastuzumab-related cardiotoxicity per month Palliative trastuzumab, per case	TC course, FEC-D course, febrile neutropenia, AMD/MDS, and chemo-related nausea and vomiting from previous literature [209, 210], 12 months adjuvant trastuzumab from previous literature [226], local recurrence, distant recurrence and post-recurrence follow-up from previous literature[223], chemo-related CHF from previous cost-effectiveness analysis [227], and palliative trastuzumab from the literature [228]	40 years 50 years 60 years 70 years 80+ years	Not reported
Sen, Wang [193]	**Treatments** No RT EBRT IMRT Brachytherapy **Health states** Recurrence, mastectomy Metastatic care Continued phase	SEER-Medicare Previous costing study [229]	70, 75, and 80 years	70-74 years; 75-79 years; 80-94 years

Author, year	Inclusions	Data source	Age of target population	Mean age of estimation sample
	Death, the last year of life			
Desch, Hillner [197]	**Health states** Chemotherapy, if given **Side effects** Minor toxicity Major toxicity	Previous literature [224] Medical College of Virginia and estimates from Medicare data (1989)	60 years 65 years 70 years 75 years 80 years	Not reported
Direct and indirect cost				
Ward, Vicini [195] and War *et al.* (2019) [196]	**Treatments** Radiation Therapy Anastrozole (per year) Indirect costs of RT Indirect costs of Endocrine Therapy (Annual) **Health states** Salvage Mastectomy Salvage Lumpectomy or Axillary Dissection Metastatic Disease (per year)	ASCO and National Cancer Centres Network (NCCN) guidelines, all costs were adjusted to 2019 dollars using the US Bureau of Labor Statistics overall Consumer Price Index inflation	70 years or older	Not reported

(Note) AC: adriamycin, cyclophosphamide; CMF: cyclophosphamide, methotrexate, and 5-fluorouracil; HRT: tamoxifen hormone therapy; AWP: Average Wholesale Prices; PHS: Public Health Service; EBRT: external beam radiation therapy; RT: radiation therapy; IMRT: intensity-modulated RT

3.5 Discussion

Decision-analytic model-based economic evaluations will help inform the growing interest from decision-makers and clinicians about how best to treat older patients diagnosed with primary breast cancer. However, this review found just seven economic evaluations of treatments for this older population, and all studies compared post-surgical adjuvant strategies only [191, 193-197, 199]. The authors of these economic evaluations used different methods to estimate input parameter values for HRQoL, the natural history of breast cancer, relative treatment effects, and resource use by data from both older and younger patient populations. Therefore, a gap in economic evidence exists between clinical and policy decision-making and routine clinical practice for older patients. To help close this evidence gap, the different methods to estimate age-specific input parameters reported in this review can inform the design of future model-based economic evaluations and strategies to overcome the relative scarcity of data from older patients.

A critical distinction between the identified economic evaluations was whether they reported cost-effectiveness evidence for older patients as the base-case analysis or as a subgroup analysis. For example, over half (57%) of economic evaluations in this review reported a subgroup analysis for patients older than 70 years old. Subgroup analyses in economic evaluations are a valuable method to investigate heterogeneity in cost-effectiveness by identifiable patient characteristics [230]. However, ensuring that input parameter values are appropriate for each subgroup under investigation is vital. If future economic evaluations report age-specific subgroup estimates for older patients with primary breast cancer, decision-makers and analysts should appraise whether the input parameter values are expected to vary across age groups or are independent of age. This will improve the face validity of the model-based analysis and the external validity of the subgroup cost-effectiveness estimates.

Depending on the decision problem, older patients' natural history of breast cancer may be available to estimate transition probabilities between health states. However, most economic evaluations in this review used evidence from a younger population to estimate these natural history parameters. The calibration method by Ward et al. [195, 196], which adjusted estimates from younger patients to be appropriate for an older population, is helpful for future economic evaluations when data from patients over 70 years old are unavailable. Alternatively, future economic evaluations could use formal expert elicitation methods [231] to estimate these natural history parameters with sensitivity analyses around plausible values. There has also been an increase in the availability of linked primary care, secondary care, mortality, and cancer register data sources [232]. These linked data could also be a valuable source of evidence to estimate the natural history of breast cancer for older patients in routine practice, ensuring that any selection bias and confounding are accounted for.

Older patients consume more healthcare resources than younger patients [233]. Cost studies from the US and UK [234, 235] indicated that the main cost drivers for cancer treatment in older populations were from treating side effects and related health care (for example, care and management of chemotherapy-induced neutropenia, radiotherapy-induced skin/gastrointestinal reaction, and trastuzumab induced cardiotoxicity). It is essential for future economic evaluations of treatments for primary breast cancer to report the evidence sources for resource use transparently to help decision-makers appraise whether these data can be generalised to an older population.

Sen *et al.* [193] undertook a matched cohort study to estimate the incremental cost of managing older patients with primary breast cancer. Future research could use a

matched cohort design to estimate valuable resource use data for older patients with primary breast cancer using large national observational datasets which link secondary care resource use with cancer diagnosis data. These patient-level data could then provide a better characterisation of how parameter uncertainty in estimates of resource use is distributed.

Health state utility values are a challenging input parameter in the identified studies. Almost all the studies used utility values from the utility measured from a younger population. The NICE Decision Support Unit and the International Society for Pharmaceutical Outcomes Research advise that HRQoL should be estimated using evidence from a similar population (for example, age, sex, and disease severity) to the modelled population [236, 237]. Age is a crucial determinant of HRQoL because older patients may have lower values than younger patients due to comorbidities and frailty [238]. In this review, the methods used by Ward *et al.* [195, 196] and Sen *et al.* [193] to estimate HRQoL (i.e. disutility multipliers or additive utility decrements informed by baseline values from representative surveys of the general population) are helpful techniques for future economic evaluations to incorporate age-specific input parameter values when only data from younger patients are available.

Peasgood *et al.* [239] report a systematic review and meta-regression of health state utility values for breast cancer. Many economic evaluations have previously obtained relevant input parameter values from this study. A meta-regression could be developed further by investigating whether including the mean age of the patients in each study affects the estimated relationship between health state utility and the other variables. Therefore, a systematic review and meta-regression of health state utility value in the thesis were undertaken to summarise the utility values for older women with early-stage

breast cancer and to further quantify decrements of utility values associated with age increasing for older women with early-stage breast cancer (Chapter 4).

The magnitude of the estimated relative treatment effects and toxicity for patients with breast cancer can vary by age and type of treatment [240]. For example, chemotherapy and radiotherapy have shown limited survival benefits for older patients with primary breast cancer than their younger counterparts [240]. Similarly, the effectiveness of endocrine and biological therapy is highly associated with the level and sensitivity of hormone receptors and HER-2 receptors (Chapter 2). Older patients have a higher level of ER and PR receptors, whereas they have a lower level of HER-2 receptors [58, 60] (Chapter 2). Therefore, the treatment strategy relevant to the target population should be considered in the economic evaluation to avoid overestimating the treatment effect, resources use and cost, or underestimating the quality of life.

For future economic evaluations, the target population should be defined clearly in terms of whether a patient's age interacts with the biological mechanisms of disease and, consequently, whether the estimated treatment effects are appropriate for that population. First, based on the national audit of breast cancer in older women (2022), a proportion (24%) of older women with early-stage breast cancer who are physically fit for surgery did not receive surgery instead of receiving PET in England. The value of implementation analysis can be conducted based on an economic evaluation in older patients who are fit for surgery but receiving PET to quantify the health forgone from PET (Chapter 5). Second, the choice of the target population for the comparator should also be limited to the relevant population in routine practice. For example, older patients who are physically unfit for surgery due to comorbidity or frailty may be the most appropriate population who receive PET (Chapter 7).

One limitation of this review was that the search strategy only identified published economic evaluations from peer-reviewed academic journals and may have missed some economic evaluations from government or private organisations in the grey literature. However, the sample of included studies successfully identified a broad range of methods used to estimate input parameter values for an older population. A second potential limitation was that this systematic review focused only on four specific input parameter types. Therefore, valuable methods to estimate other input parameter types may have been omitted. However, the focus on input parameters for HRQoL, the natural history of the disease, treatment effects, and resource use was sufficient to characterise the majority of essential input parameters for any model-based cost-effectiveness analysis.

3.6 Conclusion

The number of patients over 70 diagnosed with primary breast cancer is increasing. Health economic evidence will be essential to inform how best to manage these patients. This systematic review found only eight CEAs for this older population, indicating that the Markov model is the most widely used model to estimate cost-effectiveness. Although no CEA used the evidence source from older women to estimate all input parameters for modelling, there are feasible methods to adjust input parameters to fit the target population. Health state utility values are the most challenging input parameters in all the studies because there was a lack of studies measuring the values for the older population, which was further evaluated in Chapter 4. Also, well-designed observational studies using national register data and formal expert elicitation exercises present a considerable opportunity to improve the quality of input parameter estimates for this older patient population.

Chapter 4 The impact of age on health utility values for older women with early-stage breast cancer

Chapter 4 presents a systematic review and meta-regression to summarise the health state utility values for postmenopausal women with early-stage breast cancer and to quantify the association of utility values with age increase to inform the following economic evaluation. This chapter structures according to the following sections: introduction (Section 4.1), aim and objectives (Section 4.2), methods (Section 4.3), results (Section 4.4), discussion (Section 4.5) and conclusion (Section 4.6). The published manuscript of the chapter is included in Appendix 8.

4.1 Introduction

Health state utility values (HSUVs) quantify preference for specific health states and are a vital source of evidence for health economic evaluations to inform resource allocation decisions and treatment recommendations [241]. Best practice guidance explains how the most relevant HSUVs to inform decision-making should reflect the health characteristics of the target patient population [236, 242]. To improve the accuracy of HSUVs for specific populations, there is a growing focus on investigating how the impact of age is quantified across different health conditions [243]. Health conditions, such as breast cancer, are increasing in older patients due to an ageing population [22]. Considering this trend, there is a need to improve the robustness of HSUV estimates and strengthen the evidence base to support treatment recommendations in these older patient populations.

The quality of life of women with breast cancer varies with different factors. The HSUVs used in economic modelling must reflect the target population's relevant disease health states, treatments received, and patient characteristics [244]. Age is a crucial risk factor influencing the incidence and treatment of female breast cancer [245]. One-third of new

breast cancer cases in England were diagnosed at an older age (> 70 years) [25]. Older age typically corresponds with lower HSUVs due to weaker physical functioning and multimorbidity [246, 247]. However, few health economic evaluations for older women with breast cancer used HSUVs measured directly from patients aged 70 years or older.

In 2022, a systematic review identified seven economic evaluations of breast cancer treatments for older women [15]. Most studies in this review (n=6; 86%) sourced health utility data from patients younger than 70 and adjusted these estimates to correspond with an older population. A better understanding of the health utility values available in this growing patient population will be valuable to support the need for economic evidence designed to inform the management of older women with early-stage breast cancer.

A systematic review and meta-regression by Peasgood *et al.* (2010) [239] synthesised health utility values for early-stage and metastatic breast cancer. Similarly, Kaur *et al.* (2022) [248] report a meta-regression of health utility values across different stages of breast cancer and treatment. Both studies demonstrate the value of meta-regression to establish whether patient-level and treatment-related variables are associated with mean HSUVs. Although these analyses included several variables associated with health utility (for example, disease health state, treatment, and HSUV valuation method), age was not an independent variable in either meta-regression. This specification may overestimate the health utility decrement associated with disease progression. To improve the usefulness of these estimates for generating future economic evidence, including age as an independent variable within a meta-regression will help to estimate its impact on HSUVs for older women with breast cancer.

4.2 Aim and objectives

The study aimed to identify the availability of and the subsequent impact of age on HSUVs measured by EQ-5D for older women with early-stage breast cancer. To achieve the aim, there were three objectives, including (1) identify studies that estimated HSUVs by EQ-5D in a sample of postmenopausal women with early-stage breast cancer; (2) describe and appraise the quality of HSUV estimates in the subgroup of studies that focussed on older women (aged ≥ 70 years); and (3) evaluate how age affects that statistical association between HSUVs and other relevant variables.

4.3 Methods

A systematic review to identify all published studies reporting HSUVs for postmenopausal women with early-stage breast cancer was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA 2020) [185] (Appendix 9).

The protocol for this systematic review is registered at PROSPERO (no. CRD42021232743). After registration, a minor revision was made to include only studies that measured HSUVs by an EQ-5D instrument to avoid duplication with another systematic review by Kaur et al. published in 2022 [248]. EQ-5D is the generic multi-attribute measure of health status used most often by health technology assessment bodies worldwide. Hence, focusing on the EQ-5D instrument makes this study valuable for healthcare decision-makers [249].

4.3.1 Inclusion and exclusion criteria

Studies were included if they (i) reported an original HSUV for a specific health state for postmenopausal women with breast cancer, e.g., stable (defined as cancer that does not worsen after treatment, or diagnosed as stage I or II), progressed (tumour locally spread or diagnosed as stage III), or advanced disease states (distant tumour metastases or

diagnosed as stage IV), (ii) measured using an EQ-5D instrument (EQ-5D-3L or EQ-5D-5L) and valued with a tariff that is used routinely for decision-making, and (iii) were written in English (Table 4.1). Postmenopausal women as the target population were initially identified by whether the study self-reported the term “postmenopausal women” or not. If not, the cut-off age $\geqslant$ 45 years was used to define post-menopause, according to the National Health Service (NHS) in England [23].

Table 4.1. Inclusion and exclusion criteria for the study

Component	Inclusion criteria	Exclusion criteria
Population and conditions	Postmenopausal women with (operable, Stage I, Stage II, or early stage) breast cancer	• Only premenopausal women • Only male breast cancer • Only metastatic breast cancer • Unconfirmed breast cancer • Other diseases
Intervention & Comparator	Any intervention for breast cancer	No restriction on the intervention
Outcome	Studies reported at least one original utility value measured by EQ-5D (3L or 5L)	• No original utility value was reported. • Unspecified/not clearly specified health states relating to breast cancer. • Psychometric validation studies. • Description of health states without interval properties rather than the valuation of health states. • EQ-5D-5L England tariff.
Language	English	Other languages without English translation.
Publication	Full-text article	Conference abstract or proceeding, abstract without full article, letter to editors, editorial, commentary, and news.

(Note) The criteria for inclusion and exclusion were based on the PICO framework [186].

4.3.2 Literature search

Relevant studies that met the inclusion criteria were identified in two stages. In the first stage, studies published from inception to 2009 were identified from the systematic review by Peasgood *et al.* (2010) [239]. The review by Peasgood *et al.* (2010) [239] comprehensively searched thirteen databases to identify HSUVs for breast cancer measured using preference-based instruments and Google Scholar as a supplementary data source to identify the target literature. The search strategies in review by Peasgood *et al.* (2010) [239] were developed from a previously published systematic review by Hind

et al. (2010) [250] for early breast cancer. The systematic review by Hind *et al.* (2010) [250] was a part of the evidence appraisal for the NICE technology assessment for early-stage breast cancer, which had a reliable quality to identify the relevant breast cancer studies. These two reviews have been highly cited in other published reviews or original studies as data sources [251-256]. The review by Peasgood *et al.* (2010) was considered a good data source for identifying the studies on HSUVs in breast cancer before 2009. From this initial set of references, studies that reported HSUVs measured using an EQ-5D instrument were identified and retrieved for full-text review.

In the second stage, studies published from 2009 until 21 September 2021 were identified from electronic medical databases by applying structured search strategies to Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions ® 2009 January to 2021 22 September and Ovid EMBASE® from 2009 January to 2021 22 September. The search strategies (Appendix 10) included relevant terms for breast cancer used by Peasgood *et al.* (2010) [239] and HSUVs. Terms to identify HSUVs were sourced from the electronic database search filters reported by the Centre for Reviews and Dissemination [257].

4.3.3 Study selection

The titles and abstracts of studies identified from the electronic database search were screened independently by three investigators (SB, MA, YW) against the inclusion criteria. The concordance between reviewers was calculated by three pairwise intra-class correlation coefficients (ICC) [258]. ICC values less than 0.5, between 0.5 and 0.75, 0.75 and 0.9, and greater than 0.90 indicate poor, moderate, good and excellent reliability, respectively [259]. Three investigators (SB, MA, YW) independently reviewed the full text of eligible studies. The reasons for exclusion were documented and reported. Discrepancies were resolved through consensus with other reviewers (SG and LCC) to

finalise the selection of studies. This was done to ensure the reviewers appropriately applied the inclusion and exclusion criteria in the screening process.

4.3.4 Data extraction

Three reviewers (SB, MA, YW) independently extracted data from the included studies using a pre-designed data collection form and then merged by YW for analysis. Extracted data included three sections: (1) characteristics of the study, i.e., the author, year and country of the study; (2) methods of health utility valuation, i.e., the mean age of estimation sample, instrument to measure health utility values (EQ-5D-3L or EQ-5D-5L), the valuation tariff, and the sample size of the study; and (3) estimated health utility values for specific health states (stable, progression and advanced state), i.e., mean utility value, standard deviation (SD) or 95% confidence interval. Studies that estimated utility values with the EQ-5D-5L tariff for England [260] were excluded because the NICE guidance does not recommend using the tariff due to concerns about data collection and analysis methods [261]. In such circumstances, studies that estimated UK EQ-5D-3L utility values from EQ-5D-5L profiles by a recommended mapping method were included [262].

4.3.5 Data synthesis

Descriptive statistics were first used to present the included studies, study characteristics, mean, SD, median (interquartile range, IQR), and the range of the HSUVs. These results were summarised narratively, presented graphically, and stratified by different health states and treatments where possible for the full sample of postmenopausal women. For studies that did not report the SD, the estimated standard deviation was calculated from the mean value, sample size, and 95% confidence intervals based on the method suggested by the Cochrane Library [263].

The subgroup of studies which estimated HSUVs using a sample of older women (mean age ≥ 70 years) were described by the study design, country, mean age of respondent, elicitation method and quality appraisal. As there are no agreed criteria to appraise the quality of HSUVs [25], four study quality-associated questions (in Table 4.4) in this review were used to appraise the study quality for the older population. These four questions were identified from an appraisal tool (including 17 questions) developed by Nerich et al. (2017) [264] (Full appraisal tool in Appendix 11). According to a systematic review by Zoratti *et al.* [265], these four questions from the tool developed by Nerich et al. (2017) [264] helped appraise the quality of breast cancer HSUVs. YW independently appraised the quality of studies, and the appraisal results were categorised as yes (complete), yes (partial), no, and not assessable. Publication bias for HSUVs is challenging to determine because they are usually reported as secondary outcomes. Thus, publication bias in this review was not assessed.

The HSUVs were synthesised by a meta-regression following the methods used by Peasgood et al. (2010) [239] to identify the association between HSUVs and different independent variables. A linear regression model was used with the mean HSUV from each study as the dependent variable. Age is a critical factor that influences HSUVs. Therefore, this study compared the results from two regression specifications. The first specification included the reported mean age of the estimation sample for each HSUV as a continuous independent variable. The second specification omitted the reported mean age from the set of independent variables. The performance of these two specifications was compared using the coefficient of determination (R2) to assess the goodness of fit.

According to Peasgood et al.'s review [239], besides the age of the target population, several factors that may influence the HSUV measurement and valuation were included in the analysis, i.e., disease health state, the instrument to measure health utility,

treatment received, and valuation time. Disease health state (stable, progressed disease, or advanced disease states), an instrument to measure health utility (EQ-5D-3L or EQ-5D-5L), treatment received (surgery, surgery alone with adjuvant therapies, or unspecified treatment), and valuation time (less or more than one year after diagnosis) were measured as categorical variables. 'Surgery' comprised different types of surgical intervention (for example, mastectomy or breast-conserving surgery) to reduce the number of independent variables in the meta-regression, following the approach by Kaur *et al.* [248].

Other study characteristics (e.g., country of the study, valuation tariff, trial or observational study design, intervention and comparators) were not included as independent variables in the meta-regression. Given the sample size of the meta-regression, this decision was made to prevent collinearity between categorical independent variables. The regression model is weighted by the inverse of the SD for each HSUV. This approach gives greater weight to HSUVs values with a smaller SD because they offer better precision in the true utility value than those with a larger SD. Cluster-robust standard errors accounted for within-study correlation because some studies contributed more than one HSUV to the meta-regression, which was likely to be correlated [266]. The meta-regression was performed using Stata 14.0 (Stata Corp, College Station, TX) [267].

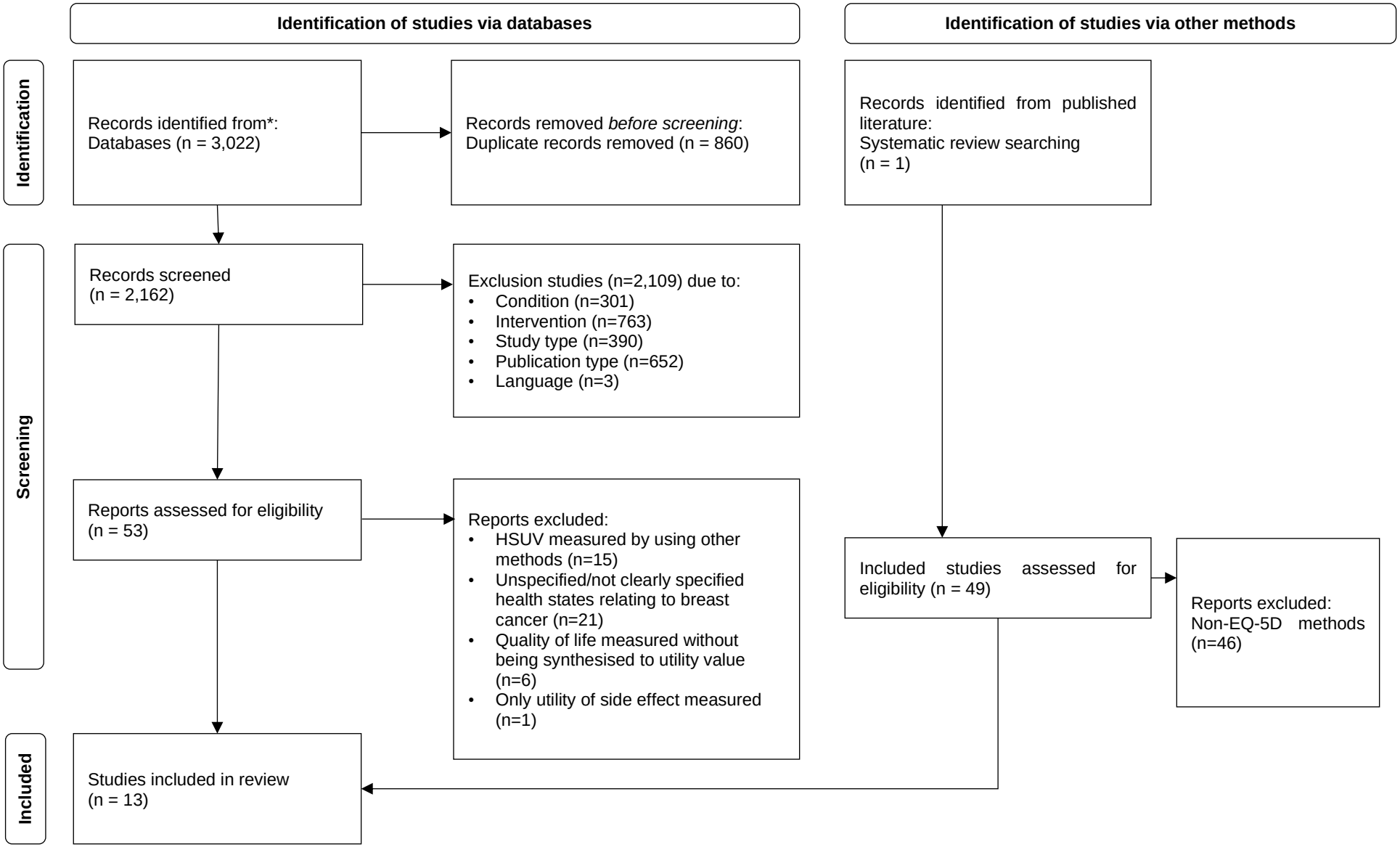
4.4 Results

4.4.1 Selection of studies

Forty-nine potentially eligible articles were identified from the systematic review by Peasgood et al.[239], and 3,022 articles were identified from the electronic medical database search. Thirteen studies met the inclusion criteria and were included in the systematic review. The reasons for exclusion are summarised in Figure 4.1. The ICC

value indicated good and excellent reliability between reviewers (pairwise ICCs between three reviewers were: 0.78, 0.89 and 0.96).

Figure 4.1. PRISMA flow diagram for selection of studies



4.4.2 Study characteristics

Fifty HSUVs were identified from the 13 included studies [268-280] (Table 4.3). The HSUVs were distributed across three health states: stable (n=33), progressed disease (n=10), and advanced disease (n=7). The EQ-5D-3L (n=43) [268-277, 279] instrument was used more often than the EQ-5D-5L instrument (n=7) [278, 280]. Six different valuation tariffs were applied across the sample, including the UK 3L (n=28) [268-270, 272, 273, 277, 279], the US 3L (n=2) [271], Canada 3L (n=4) [276], Korea 3L (n=5) [275], China 3L (n=4) [274], China 5L (n=4) [278], and Indonesian 5L (n=3) [280] tariffs (Figure 4.2). Across the whole sample, these HSUVs were estimated from patients with a mean age between 44 and 75 years. One study defined their sample as 'postmenopausal women' [280]. The remaining studies (92%) had a sample of women whose mean age was over 45 (Reason for exclusion in Table 4.2).

Table 4.2. Reasons for excluding studies

Exclusion	Reasons	Number
Condition	Only premenopausal	10
	Only metastatic breast cancer	212
	Unconfirmed breast cancer	6
	Other diseases	73
Intervention and comparator	Cancer-related symptoms assessment without health state-reported	173
Outcomes	No original utility reported or from previous literature	541
	Unspecified/not clearly specified health states relating to breast cancer	59
	Quality of life measured without being synthesised to utility values	31
	Only the utility of side effects measured	2
Study type	Psychometric validation studies	198
	Description of health states without interval properties rather than the valuation of health states	192
	Non-Eq-5D method in the review by Peasgood	46
Publication	Conference abstract or heading or letters	652
Language	Language	3

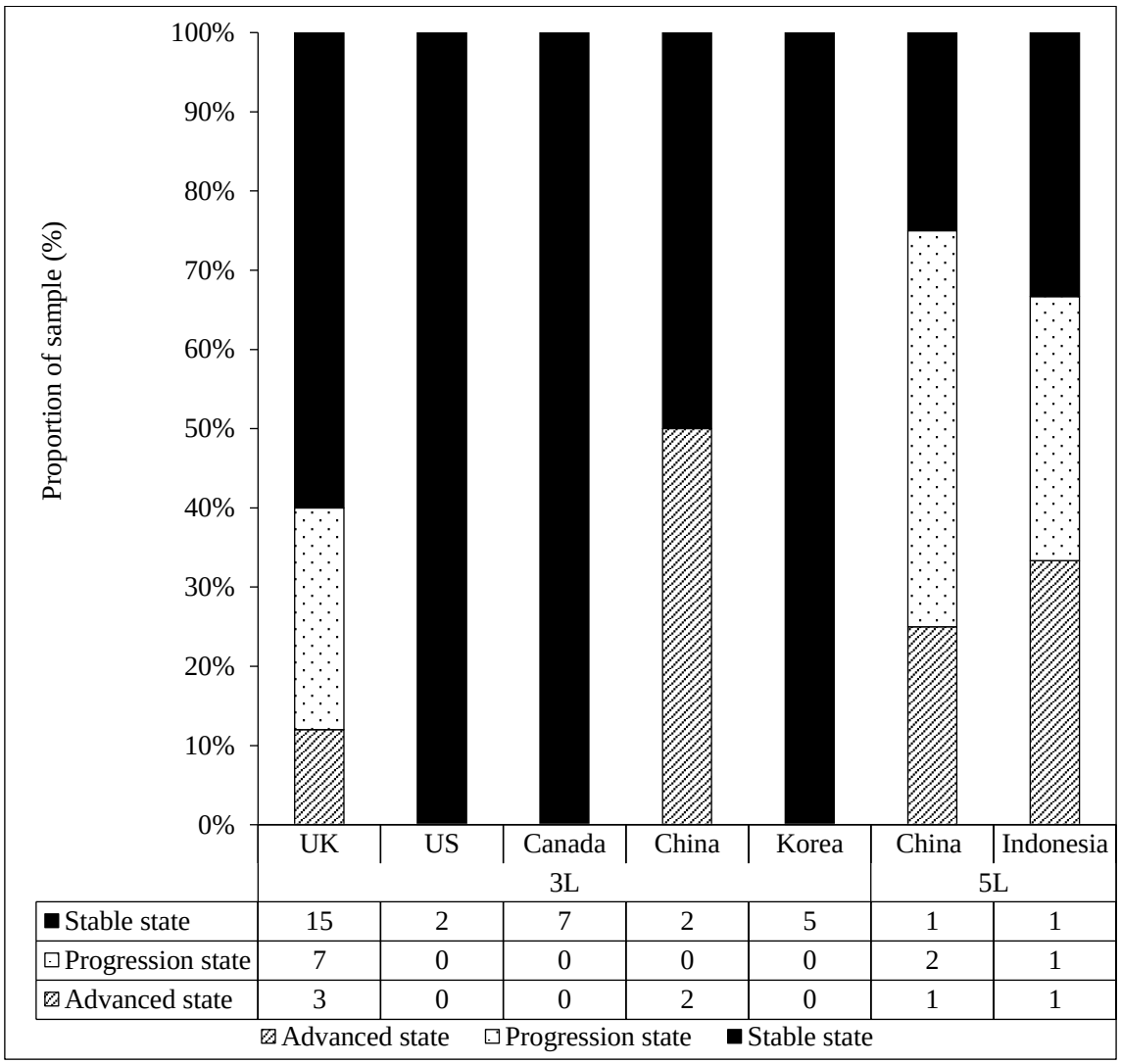
The subset of health utility values for the stable state (n = 33, same mean and median: 0.83; range: 0.67 to 0.92) were higher than the progressed disease state (n = 10, mean: 0.79; median: 0.77; range: 0.72–0.94) and advanced disease state (n = 7, mean: 0.68; median: 0.69; range: 0.55–0.85) (Figure 4.3). (All the mean HSUVs extracted in Appendix 12)

Table 4.3. Characteristics of identified studies (n=13)

Author	Country	Study period	Study type	Respondent	Method of valuation	Valuation Tariff	Mean Age	Sample size
EQ-5D-3L								
Conner-Spady *et al.* (2005) [268]	Canada	04/1995-10/1998	Questionnaire	Patients' own health	EQ-5D-3L	UK	44.7	52
Lidgren, et al. (2007) [269]	Sweden	04-05/2005	Questionnaire	Patients' own health	EQ-5D-3L	UK	57	345
Kimman et al (2009) [270]	Netherland	07/2005-09/2007	Questionnaire	Patients' own health	EQ-5D-3L	UK	55.8	192
Freedman *et al.* (2010) [271]*	USA	2010	Questionnaire	Patients' own health	EQ-5D-3L	US	45-64	1050
Williams, et al. (2011) [272]	UK	1997	Questionnaire	Patients' own health	EQ-5D-3L	UK	72.8	255
Yousefi, *et al.* (2016) [273]	Iran	11/2013-06/2014	Questionnaire	Patients' own health	EQ-5D-3L	UK	46.7	163
Wang, *et al.* (2018) [274]	China	12/2016-03/2017	Questionnaire	Patients' own health	EQ-5D-3L	China	49.1	2828
Yu, *et al.* (2018) [275]	Korea	01/2012-06/2012	Questionnaire	Patients' own health	EQ-5D-3L	Korea	48.9	226
Sattar, *et al.* (2019) [276]	Canada	10/2014-10/2015	Questionnaire	Patients' own health	EQ-5D-3L	Canada	75.3	58
Tanaka, *et al.* (2019) [277]	Japan	Not stated	Questionnaire	Patients' own health	EQ-5D-3L	UK	53.4/57.6	38
Zigman, *et al.* (2020) [279]	Croatia	01/2016-12/2016	Questionnaire	Patients' own health	EQ-5D-3L	UK	44.7	114
EQ-5D-5L								
Yang, *et al.* (2020) [278]	China	08/2017-05/20	Questionnaire	Patients' own health	EQ-5D-5L	China	51.37	446
Etikasari, *et al.* (2021) [280]	Indonesia	01/2019-08/2019	Questionnaire	Patients' own health	EQ-5D-5L	Indonesian	59.2	126

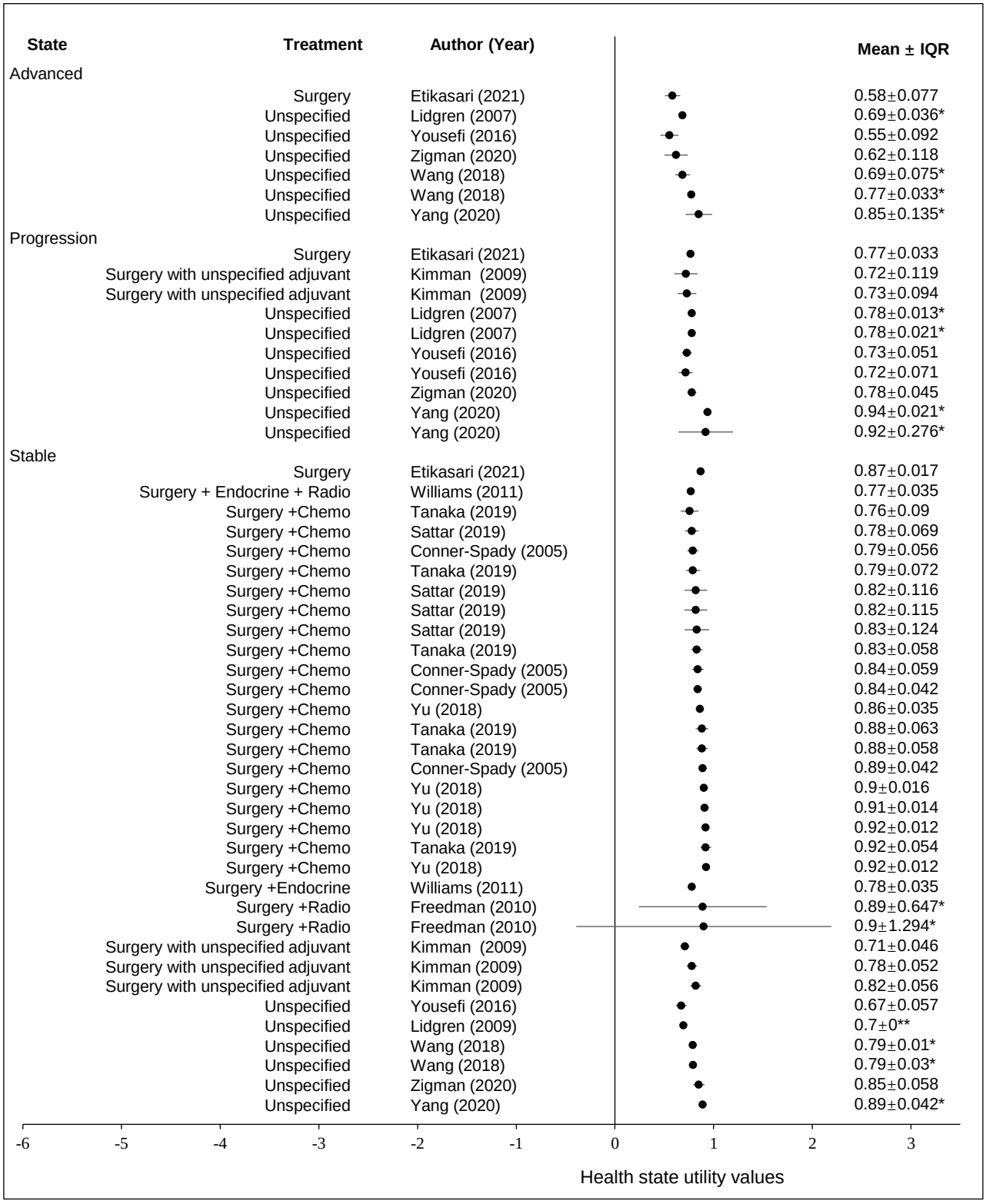
(Note) * Respondent age in Freedman [271] was 45-64 years (57%); VAS: Visual analogue scale SG: Standard gamble; SF-6D: Short-Form Six-Dimension; TTO: Time trade-off; EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire.

Figure 4.2. Health state utility values sample by health state and valuation tariff



	UK	US	Canada	China	Korea	China	Indonesia
	3L					5L	
Stable state	15	2	7	2	5	1	1
Progression state	7	0	0	0	0	2	1
Advanced state	3	0	0	2	0	1	1

Figure 4.3. Health state utility values by health state



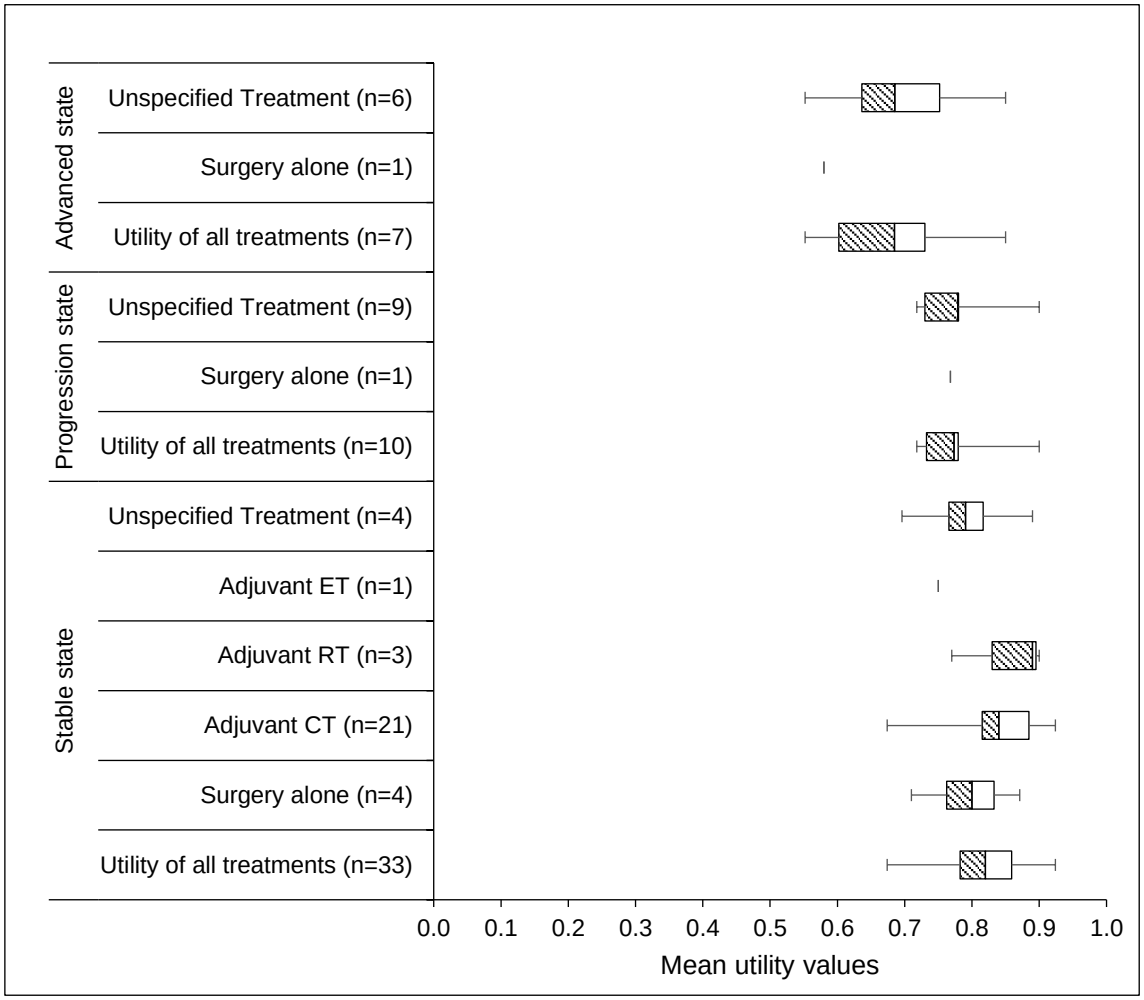
(Note) Bars present the interquartile range; IQR: interquartile range; *: standard deviation estimated; **: no standard deviation reported or standard deviation cannot be estimated.

Chemo: chemotherapy; Radio: radiotherapy; Unspecified: treatment unspecified

Figure 4.4 (a box-and-whisker plot) reports the distribution of HSUVs by disease state and treatment received. Of the 33 utility values for the stable health state, treatment was not specified for six utility values (mean: 0.78; median: 0.79; range: 0.67-0.89). Patients who received surgery with adjuvant radiotherapy had the highest utility value (n = 3; mean: 0.86; median: 0.89; range: 0.78–0.90), followed by surgery with adjuvant chemotherapy (n = 19; mean: 0.85, median: 0.84; range: 0.76-0.92) and surgery alone (n = 1) or with unspecific adjuvant treatment (n = 3; same mean and median: 0.80; range: 0.71–0.87).

It was impossible to stratify HSUVs by treatment for progressed and advanced health states, as only one HSUV specified treatment with surgery alone in both the progressed state (0.77) and advanced disease state (0.58). The remaining values for these two health states were not attached to a specific treatment. The mean of these remaining HSUVs was 0.79 for the progressed state (n = 9; median: 0.78; range: 0.72–0.94) and 0.69 for the advanced state (n = 6; median: 0.69; range: 0.55–0.85) (Figure 4.4).

Figure 4.4. Utility values for three health states stratified by treatment



(Note) In the box and whisker plot, the bottom and top of the box are the 25th and 75th percentile. The middle band of the box is the 50th percentile (the median). The top and bottom lines indicate the minimum and maximum values. Adjuvant treatment is given post-surgery; CT: Chemotherapy; RT: Radiotherapy; ET: Endocrine therapy.

4.4.3 Quality appraisal of studies measuring HSUV in older women

There were 6 HSUVs for the stable disease state explicitly estimated from a sample of older patients (mean age >70 years) in two clinical trials by Williams et al. (2011) [272] (n=2) and Sattar et al. (2019) [276] (n=4). These two studies are now described in further detail. The quality appraisal criteria are reported in Table 4.4.

Williams *et al.* (2011) [272] conducted a clinical trial in the UK with 248 older participants (mean age: 72 years, SD: 5) who had primary breast cancer and received surgery or adjuvant endocrine therapy with or without radiotherapy. The duration of follow-up was

five years. The EQ-5D-3L instrument and UK tariff [281] were used to estimate the HSUVs. Across both arms, 12 HSUVs were estimated at baseline and 3.5, 9, 15, 36, and 60 months after surgery. The specific health state associated with these HSUVs was not reported. Assuming that patients were stable within six months after surgery, at 3.5 months, the HSUVs for adjuvant endocrine therapy alone was 0.77 (95%CI: 0.74 to 0.80), and for adjuvant endocrine therapy plus radiotherapy was 0.78 (95%CI: 0.75 to 0.81).

Sattar *et al.* (2019) [276] conducted a clinical trial in older participants with breast cancer who received surgery and adjuvant chemotherapy with (n = 30, mean age: 75 years) and without (the usual care; n = 28, mean age: 75 years) a geriatric assessment in Canada. The EQ-5D-3L instrument and Canadian tariff [282] were used to estimate the HSUVs. Across both arms, eight HSUVs were estimated at baseline and 3, 6, and 12 months. The specific health state associated with these HSUVs was not reported. Assuming that patients were stable within 6 months after surgery, the median HSUVs for patients with the geriatric assessment at 3 and 6 months were 0.82 (IQR: 0.29) and 0.82 (IQR: 0.27), respectively. The median HSUVs for patients without the geriatric assessment at the same periods were 0.78 (IQR: 0.15) and 0.83 (IQR: 0.22).

Table 4.4. Quality appraisal of two studies for older women

Questions	Williams et al. (2011) [272]	Sattar *et al.* (2019) [276]
Is an explanation provided for the choice of technique(s) used to elicit HSUVs?	Complete	Partial
Is a comprehensive description provided of the technique(s) used to elicit the obtained HSUVs?	Complete	Complete
Is an explanation provided for the choice of the population used to elicit HSUVs (i.e., patient, healthcare professional [and type], expert, general population)?	Partial	Complete
Is a comprehensive description provided for the population used to elicit HSUVs (i.e., characteristics, size, and nationality)?	Complete	Complete

(Note) Complete: Yes (complete); Partial: Yes (partial); Appraisal questions extracted from the study by Nerich *et al.* (2017) [264].

Both studies completed or partially reported four questions of the quality appraisal (Table 4.4). Williams *et al.* (2011) [272] reported that the reason for selecting the EQ-5D-3L instrument to measure the HSUVs was due to the recommendations by the NICE reference case. They thoroughly explained that the reason for using the EQ-5D-3L UK valuation tariff. Both studies [272, 276] fully reported details about the characteristics of the study population as they were randomised control trials. Therefore, the two studies [272, 276] are high-quality based on this quality appraisal tool.

4.4.4 Regression analysis

Table 4.5 reports the results of the meta-regression analyses. The specification that included age as an independent variable had better goodness of fit (R2 increased from 0.686 to 0.691). Across all model specifications, the variables for disease health state, treatment, and instrument to measure HSUVs had a statistically significant ($p < 0.05$) association with the mean HSUV. Age was estimated to have a negative but non-statistically significant coefficient (-0.001, 95%CI: -0.004 to 0.002). This result indicates that expected HSUVs reduce as postmenopausal women with breast cancer age. The statistically significant and negative coefficients on progression (-0.052) and advanced disease states (-0.143) indicated that expected HSUVs reduce as the disease worsens. Compared with surgery alone, adjuvant treatments improved the mean HSUVs with an increment of 0.205 for adjuvant chemotherapy, 0.200 for adjuvant radiotherapy, and 0.085 for adjuvant endocrine therapy. The HSUV for patients over one year after treatment was 0.045 units higher than those who received treatment within one year.

Table 4.5. Regression model for values

Variables	Age-adjusted			No age-adjusted		
	Coefficient (95%CI)	**SE**	**p-value**	**Coefficient (95% CI)**	**SE**	**p-value**
Age	-0.0013 (-0.004, 0.002)	0.001	0.469	-	-	-
Health state reference: stable state (n=32)						
Progressed state (n=10)	-0.056 (-0.095, -0.016)	0.018	0.009	-0.059 (-0.100, -0.018)	0.019	0.009
Advanced state (n=8)	-0.153 (-0.256, -0.050)	0.047	0.007	-0.157 (-0.260, -0.054)	0.048	0.006
Instrument reference: EQ-5D-3L instrument (n=43)						
EQ-5D-5L (n=7)	0.176 (0.115, 0.237)	0.028	<0.001	0.176 (0.120, 0.233)	0.026	<0.001
Treatment reference: surgery alone (n=3)						
Surgery adjuvant chemotherapy (n=20)	0.200 (0.129, 0.272)	0.033	<0.001	0.205 (0.141, 0.269)	0.03	<0.001
Surgery adjuvant radiotherapy (n=2)	0.197 (0.139, 0.255)	0.027	<0.001	0.202 (0.155, 0.248)	0.022	<0.001
Surgery adjuvant endocrine therapy (n=5)	0.084 (0.035, 0.133)	0.023	0.003	0.084 (0.039, 0.129)	0.021	0.001
Surgery without specified adjuvant (n=19)	0.109 (0.076, 0.141)	0.015	<0.001	0.116 (0.091, 0.141)	0.011	<0.001
Unspecified treatment (n=1)	0.120 (0.055, 0.185)	0.030	0.001	0.107 (0.044, 0.171)	0.029	0.003
Valuation time reference: less than one year (n=19)						
Over 1 year (n=31)	0.043 (0.005, 0.082)	0.018	0.03	0.049 (0.012, 0.086)	0.017	0.014
Constant	0.702 (0.495, 0.909)	0.096	<0.001	0.643 (0.579, 0.706)	0.029	<0.001
Observations	50			50		
R-squared	0.6936			0.6903		

(Note) 95%CI: 95% confidence interval; SE: standard error.

4.5 Discussion

This study provides valuable utility values for older women with early-stage breast cancer to support future economic analyses and decision-making. Six utility values for patients with stable breast cancer, measured HSUVs from an older population with mean age $\geqslant$ 70 years, were identified from two studies conducted in the UK [272] and Canada [276]. In addition, the meta-regression quantified the disease-specific age-related utility decrement for older women with breast cancer and provided improved estimates of HSUV modifiers for age by controlling for disease state and treatment. These estimates improve the robustness of evidence for future quality-of-life research and health economic evaluations for older women with breast cancer.

There is consensus among healthcare providers that the quality of life for women with breast cancer reduces with ageing due to comorbidity and frailty related to poor physical functioning [283]. Therefore, it is necessary to incorporate this reduction of health utility within economic evaluations to improve the robustness of quality-adjusted life year (QALY) estimates [236]. The association of HUSVs with other vital factors, including treatment types (e.g., mastectomy or non-specified surgery type, adjuvant chemotherapy or radiotherapy et al.), valuation methods (e.g., EQ-5D, standard gamble, time trade-off), valuation respondents (patients, clinicians or scenario), has been comprehensively assessed by previously published studies by Peasgood *et al.* (2010) [239] and updated Kaur *et al.* (2022) [248]. Our study initially included age as a factor to quantify the association of HSUVs with age with controlling other similar variables. The meta-regression results in our review provided insights into healthcare analysts or decision-makers in future research or decision-making to improve breast cancer management in older women.

For healthcare decision-makers who use health economic evidence, decisions are made according to the incremental expected cost and health benefits of care, irrespective of

whether differences are statistically significant [168]. Therefore, although the association between age and HSUVs had no statistical difference in our analysis, there still is a significant influence on improving healthcare decision-making. First, the catalogue of EQ-5D values by Sullivan *et al*. [281] estimated an age-related utility decrement of -0.0003 in the general population. However, the results from this study indicate that the condition-specific age-related utility decrement for breast cancer has a larger magnitude (-0.0013) than for the general population. Future studies' validity to estimate the lifetime trajectory of HSUVs may be improved by using condition-specific age-related utility decrements (as part of the base case or sensitivity analysis) instead of those values estimated from the general population. Second, the utility decrement associated with disease progression may be overestimated by omitting age as an independent variable (for example, compare the utility decrements for disease states across both regression specifications in Table 4.5). Compared with other published results, the utility decrement of the progressed state compared with the stable state was -0.143 in Peasgood et al. [239] and -0.0549 in the present study.

Similarly, the utility decrement of the advanced state was -0.338 in Peasgood et al. [239] and -0.1521 in the present study. There are two main reasons to explain the differences between these estimated decrements. First, the review by Peasgood *et al.* included values measured using various preference-based instruments, while we only included HSUVs measured by EQ-5D [239]. Second, Peasgood *et al.* analysed women with breast cancer in all age groups, whereas this review focused on postmenopausal women with early-stage breast cancer [239]. These reasons led to a smaller sample size for the meta-regression than other published examples. Consequently, the results from the regression model in the present study provide relevant HSUV decrements for postmenopausal women with early-stage breast cancer for decision-makers who use an EQ-5D instrument.

Second, the utility decrement associated with disease progression may be overestimated by omitting age as an independent variable. The decrements of progressed state compared with the stable state were -0.143, reported by Peasgood [239], and decrements of -0.0549 by our analysis. Meanwhile, the decrements of advanced states were -0.338, reported by Peasgood [239], and decrements of -0.1521 in the analysis of this study.

In addition, a growing phenomenon in managing breast cancer for older women is that many patients will receive primary endocrine therapy instead of surgery as their initial treatment [9, 68]. Yet this review found no studies that estimated HSUVs for women with early-stage breast cancer who received non-surgical first-line treatment. Instead, the identified studies comprised patients who received surgery with or without adjuvant treatment. One study did not meet the inclusion criteria for this review (because HSUVs were measured using the EQ-5D-5L UK tariff) but did measure HSUVs for older women receiving primary endocrine therapy [284]. The size of the patient cohort who receive non-surgical intervention in clinical practice is likely to increase, all else being equal, as the population ages and more breast cancer cases are diagnosed at a later age [68, 285]. A greater focus on estimating health utility values for this patient cohort will be valuable to understand better how HSUVs can be affected by the direct impact of treatment-related side effects and the longer-term impact of changes in disease outcomes.

One limitation of this review was related to the search process. The search strategy only identified published manuscripts from peer-reviewed academic journals and may have missed HSUVs reported in the grey literature and other data sources. However, the results indicate that the sample of included studies may be potentially sufficient to pool and quantify the condition-specific association between age and health utility for older women with breast cancer. Searching Medline and Embase has a high ability to identify

relevant studies (Bramer *et al.* [286] report a 92.8% recall rate) and has been used effectively by other systematic reviews of HSUVs [287].

A second limitation was that only HSUVs measured by the EQ-5D instruments were included in the analysis. This may constrain the generalisability of the results because the estimated associations are not likely to apply to other preference-based instruments (such as Short Form-6 Dimension [136] or the Health Utilities Index [288]). However, the focus on EQ-5D instruments will be most valuable to healthcare decision-makers because of their widespread global use by health technology assessment bodies [249]. Finally, omitting the EQ-5D valuation tariff as an independent variable in the meta-regression is a limitation if these cross-country differences impacted the estimated mean HSUV. This impact could be explored further as more HSUVs for older women with breast cancer become available across different counties in the future.

Future research can aim to investigate the impact of age on HSUVs estimated by other preference-based instruments for older women with breast cancer and identify studies from other data sources to supplement the current results. In addition, future studies can be designed to establish whether HSUVs estimated by EQ-5D instruments are affected by the treatment received once older patients enter the progressed or advanced disease states. Finally, other chronic conditions (such as diabetes and cardiovascular disease) are becoming more common due to an ageing population [289]. Future studies can estimate the condition-specific age-related utility decrement for different diseases to improve the validity of lifetime HSUV estimates and the quality of evidence that informs healthcare decision-making.

4.6 Conclusion

This study strengthens the HSUV evidence base to help inform future decision-making regarding older women with breast cancer. Specifically, first, this systematic review

identified the useful values for the model-based economic evaluations (Chapters 5 and 7). Second, the decrements of HSUVs with age increase for postmenopausal women with early-stage breast cancer was quantified through the meta-regression, which can be used to adjust the HSUVs with age increase in the model-based economic evaluations in the thesis (Chapters 5 and 7).

The age-adjusted health utility decrements for disease states can improve the quality of crucial input parameter values for cost-effectiveness analyses of treatments for this older population. The estimated condition-specific health utility decrement will improve the validity of lifetime HSUV estimates for people with breast cancer. A greater emphasis on accounting for the impact of age on HSUVs will improve the robustness of evidence essential to guide healthcare decision-making for the growing number of older patients diagnosed with early-stage breast cancer.

Chapter 5 Cost-effectiveness of surgery compared with primary endocrine therapy and populational health forgone from the imperfect implementation of surgery in England

Chapter 5 reports the cost-effectiveness and value of information comparing PET with surgery in older women with early-stage breast cancer who are fit for surgery. This chapter reports following the Consolidated Health Economic Evaluation Reporting Standards statement recommended by the NICE guidance and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (Full statement checklist reported in Appendix 13) [189].

5.1 Introduction

As summarised in Chapter 2, although PET has been suggested to be given to older women with ER+ breast cancer who are unfit for surgery [12], there are still a proportion (76%) of older women with operable breast cancer who did not receive surgery, according to the national audit of breast cancer in older women [11]. Patient preference and clinician advice influence PET as the initial treatment in older patients. In five UK hospitals, semi-structured interviews were conducted on 33 older women with breast cancer (median age: 82; range: 75-95 years). They found that most participants preferred PET over surgery as the initial treatment due to their age and fears of surgery-related physical or mental impacts. PET was considered a less invasive treatment with minimal disruption of daily life [81]. Likewise, from 228 responses to a survey on breast surgeons (response rate: 47%) in the UK, some surgeons (7%) also recommended non-surgery (i.e. PET) to older women with early-stage breast cancer due to the risks of surgical complications and the impact on the quality of life [13]. Moreover, a systematic review and meta-analysis [94] indicated no statistical difference in overall survival between surgery and PET in operable older women with breast cancer.

However, robust economic evidence is lacking to inform clinicians, patients, and policymakers about the cost-effectiveness between surgery and PET. Following the systematic review assessing evidence sources applied to cost-effectiveness analyses for older women with early-stage breast cancer (Chapter 3), one model-based economic evaluation by Holmes *et al.* (2021) was published that compared the cost-effectiveness of PET with surgery in older women aged ≥ 70 years with early-stage breast cancer using an observational study as the data source to estimate clinical effects between surgery and PET [199]. Of this CEA, the clinical effectiveness of PET and surgery were estimated from a meta-analysis by Morgan *et al*. (2014) [94]. Overall survival of PET and surgery were estimated from a cohort study [290], which included over 3,400 UK women aged 70+ with early breast cancer with a median 52-month follow-up [290]. The results of this CEA indicated that surgery generated superior health outcomes and cost less in older women who are fit for surgery.

Nevertheless, Holmes *et al.* (2021) [199] assumed the comparative clinical effectiveness of PET compared with surgery was assumed as a constant hazard ratio of survival identified from a meta-analysis [94]. The magnitude of treatment effects between surgery and PET is not likely to be the same during survival time, which means using a consistent hazard ratio to estimate the clinical effectiveness of PET from the clinical effectiveness of surgery may be inappropriate and bias the CEA result. This approach may underestimate the clinical effectiveness of PET because the difference in treatment effects between surgery and PET may reduce with age increased. Patients receiving PET as initial treatment in routine clinical practice are generally frailer or have more comorbidities than those with surgery, which may lead to a shorter overall survival for the patients with PET. Instead, Chakrabarti ***et al.'s*** (2011) RCT with a 20-year follow-up provides a better understanding of the long-term health benefits between surgery and PET to estimate probabilities of states with time-varying individually [99]. Besides, the national audit reported that despite surgery as a cost-effective strategy in routine clinical

practice, it might not be adopted entirely as the first-line treatment for older patients with early-stage breast cancer who are fit for surgery (imperfect implementation of surgery) [11]. In this case, it is necessary to understand the economic and health forgone for patients who do not receive surgery as the initial treatment for NHS to allocate the health resource efficiently.

Therefore, this Chapter used a higher-quality data source (RCT) to develop a model-based economic evaluation to assess the cost-effectiveness of PET versus surgery in older patients who are fit for surgery. In addition, the value of implementation analysis was conducted to quantify the forgone health or benefits from PET to supplement the current economic evidence.

5.2 Aim and objectives

Chapter 5 aimed to generate economic evidence for older women with early-stage breast cancer who are fit for surgery by comparing PET against surgery using RCT as an evidence source and informing the implementation of surgery and PET. The objectives included:

(1) To assess the cost-effectiveness of PET and surgery in the target population;

(2) To estimate the value of further research;

(3) To quantify the impact of the imperfect implementation of surgery in this population.

5.3 Methods

5.3.1 Study design

This probabilistic, decision-analytic, model-based, cost-effectiveness analysis (CEA) was conducted in a Markov model comparing the lifetime cost and health outcomes of surgery alone against PET in older women with operable early-stage breast cancer. The target population was older women (aged ≥ 70 years) with unselected oestrogen receptor

status early-stage breast cancer who are fit for surgery without advanced local disease or distant metastases. Surgery was defined as mastectomy or breast-conserving surgery alone without post-adjuvant therapy. PET was defined as 20 mg of tamoxifen per day for lifetime treatment.

According to the NICE reference case, the cost was estimated from the perspective of National Health Service (NHS) England and Personal Social Services, and quality-adjusted life years (QALYs) were measured as the health outcomes. Costs and QALYs were discounted by 3.5% per year using the 2020/21 prices. The analysis was conducted according to the NICE reference case in England (Figure 5.1) [133].

Table 5.1. Decision problem addressed by the cost-effectiveness analysis

Element of decision problems	Description
Population	Older women (≥ 70 years) with early-stage breast cancer (operable patients)
Intervention	Primary endocrine therapy
Comparator	Surgery, including mastectomy and breast-conserving surgery
Perspective	NHS England & Personal Social Services perspective
Measures of health outcome	EQ-5D quality-adjusted life years
Cost consideration	Include direct medical costs: • cost of treatment • cost of hospitalisation • cost of follow-up Exclude direct non-medical, indirect and productivity cost
Outcome	• Expected incremental cost • Expected incremental QALYs • Incremental cost-effectiveness ratio • Expected values of perfect information
Time horizon	The lifetime with a 6-month cycle length
Discount rate	Cost=3.5%, QALYs=3.5%
Cost-effectiveness threshold	£20,000 to £30,000 per QALY gained
Sensitivity analysis	• one-way sensitivity analysis • probabilistic sensitivity analysis

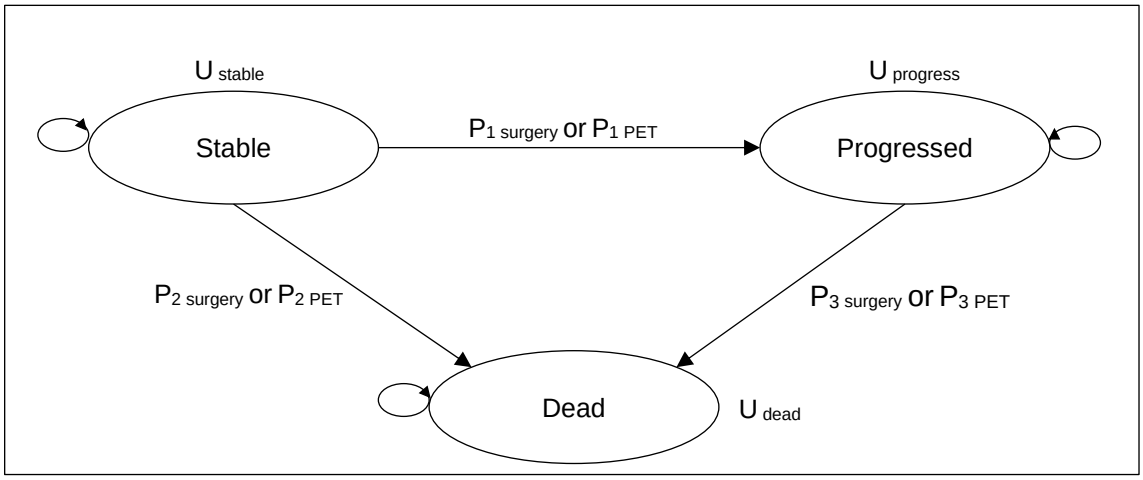
(Note) NHS: National Health Service; QALYs: Quality-adjusted life years; NHS: National Health Service.

5.3.2 Model structure

A lifetime cohort simulation used the Markov model with three mutually exclusive health states: stable (receiving treatment without local or distant progression), progressed (recurrence in the ipsilateral chest wall following mastectomy; local disease progression following PET), and dead (Figure 5.1). The Markov simulation was conceptualised and developed based on two steps, (1) a systematic review (Chapter 3) appraised the model

structure and data sources for input parameters to inform the model design, (2) and a consultation with a clinical expert (Prof Kwok-Leung Cheung), to consider the current clinical practice in the UK and the standard treatment pathway for older women with early-stage breast cancer after confirmed diagnosis in the model design. A six-month cycle length was used as two clinical events unlikely to happen simultaneously within one cycle length [291]. The input data for this Markov model consisted of the clinical effectiveness (transition probabilities between health states), health state utility values, resource use and unit cost (Table 5.3).

Figure 5.1. Model structure



(Note) The transition between states is limited to the direction illustrated by arrows. U: utility; P: probability; PET: primary endocrine therapy.

5.3.3 Clinical effectiveness

Transition probabilities from the progression-free (stable state) to progressed and dead states (P_1 and P_2 in Figure 5.1) of both surgery and PET were derived from a published RCT by Chakrabarti *et al*. (2011) [99] (Table 5.3). The RCT by Chakrabarti *et al*. (2011) [99] recruited 131 older women (aged ≥ 70 years) with early-stage breast cancer, regardless of ER status, from a single centre (the Nottingham Breast Unit in England) between 1982 and 1987. Participants were randomly assigned to the surgery arm

(wedge mastectomy alone, n=66) or PET arm (tamoxifen alone, n=65) and followed up for 20 years [99].

The RCT by Chakrabarti *et al*. (2011) [99] was identified from a Cochrane systematic review which included 6 RCTs comparing surgery with PET [94], of which, the RCT by Chakrabarti *et al*. (2011) had a 20-year follow-up [99]. Most RCTs did not have a lifelong follow-up due to financial constraints; however, longer follow-ups will reduce the uncertainty while extrapolating the treatment effects in decision modelling [292]. Furthermore, the results of this RCT by Chakrabarti *et al.* showed the same conclusion as the meta-analysis, there was no significant difference in overall survival between surgery and PET for older women [99]. Moreover, Chakrabarti *et al.*'s RCT provided not only the overall survival curves but also progression-free survival curves [99], which can estimate the transition probabilities from stable to death and progression simultaneously, thus can reduce the uncertain treatment effects estimated by using indirect measures, for example, hazard ratio between PET and surgery. Therefore, this RCT was plausible to estimate treatment effects in the cost-effectiveness analysis.

The Kaplan-Meier curves for overall and progression-free survival were reconstructed in software (DigitizeIt®) using the validated method by Guyot *et al.* [293]. Parametric survival analysis with five survival functions (Exponential, Weibull, Gompertz, Log-norm and Log-logistic functions) was performed on these data [294]. The most appropriate goodness-of-fit statistics parametric survival function was selected by reference, i.e., the lowest Akaike Information Criteria (AIC) and the Bayesian Information Criteria (BIC) values [295, 296]. Visual inspection was conducted to assess the clinical plausibility of the extrapolation [294, 297]. Gompertz distributions best fit the surgery arm's overall and progression-free survival data. Log-logistic and log-normal distributions best fit PET's overall and progression-free survival data, respectively (Table 5.3). The transition

probability over time was calculated from either the estimated hazard function [H(t)] or survival functions [S(t)] [294]. (Details of re-build KM curve in Appendix 14)

The transition probability of death from the progressed state depended on whether the patient had metastatic disease. The transition probabilities from the progressed or metastasis to the dead state were directly elicited from a previously published cost-effectiveness analysis [298]. The proportion of patients who had metastasis in the progression state (42% for the surgery arm and 35% for the PET arm) was assumed based on the RCT by Chakrabarti *et al.* (2011) [99]. The transition probabilities from the progressed (4%) or metastasis (10%) to the dead state were estimated from a previously published cost-effectiveness analysis [298].

5.3.4 Utility

Health utility values were measured by the EQ-5D-3L instrument and valued by UK tariff [299]. The EQ-5D-3L is a preferred generic instrument to value health from 0 (dead) to 1 (perfect state), and states worse than death (-0.594) are possible in England [135]. The utility value for the stable state was estimated from the RCT of 85 older patients with early-stage breast cancer (mean age: 72.3 years, standard deviation: 5.0) with or without post-surgical radiotherapy by Williams *et al.* (2011) [272]. The mean utility value and 95% confidence interval (95%CI) of surgery without radiotherapy were 0.75 (95%CI: 0.72, 0.79). The RCT by Williams *et al.* (2011) [272] was identified through the systematic review in Chapter 4.

Utility values for the progressed and metastasis states were estimated using the additive decrements method based on a systematic review and meta-regression of utility values for breast cancer (decremental values of progressed disease: -0.143; metastatic disease: -0.338) (Table 5.3) [239]. Utility values declined by 0.0013 (95%CI: -0.004 to 0.002) each

year based on a meta-regression of EQ-5D utility values in older women with early-stage breast cancer to reflect the natural decrease in quality of life as age increases (Chapter 4).

5.3.5 Resource use and cost

Healthcare and treatment resource use related to different health states in the model was estimated based on the national clinical guideline for early and locally advanced breast cancer in the UK [3] (Table 5.2). The cost for surgery was calculated by assuming there are three types of surgical treatment in different proportions: mastectomy, breast-conserving surgery and delayed breast reconstruction. According to the national audit of breast cancer in older women reported in 2021 [10], it was assumed that: (1) 35% of patients received a mastectomy and 65% of patients received breast-conserving surgery; (2) all the older patients would receive delayed breast reconstruction after the mastectomy within one year [300]. The unit cost of surgery was obtained from the England NHS reference costs (2019/2020) [301].

The cost of PET was estimated based on the assumption that patients would receive tamoxifen in the first five years after a confirmed breast cancer diagnosis and then may change to an aromatase inhibitor (i.e., letrozole) for a lifelong treatment [3]. The unit cost of treatments was obtained from the British National Formulary (BNF, November 2021, Drug Tariff).

Patients in both arms whose breast cancer progressed were assumed to receive multidisciplinary team care and other interventions (for example, chemotherapy and endocrine therapy) for breast cancer within six months (Table 5.3). The costs of progressed and metastatic states were derived from a published costing study in England, including the costs of treatment (for example, chemotherapy, endocrine

therapy, radiotherapy, and bisphosphonates) and inpatient days, in which the resource use was identified from the patient-level data sources. [302]. Historic prices presented by the British Pound of treatment and health states were inflated to 2020/21 using the inflation indices published by the Personal Social Services Research Unit [303]. All the costs were presented using the pound sterling (£).

Table 5.2. Resources use of estimation of cost for treatment and diagnosis

Health care resources	Proportion	HRG (£)	Source, Currency
Diagnosis and healthcare			
Outpatient follow-up visit	1	125	NHS reference cost 19/20, WH52A
Respite Care with a length of stay of four days or less	1	909	NHS reference cost 19/20, WH20C
Malignant Breast Disorders with Interventions, with CC Score 0-2	1	1375.11	NHS reference cost 19/20, JA12F
Malignant Breast Disorders without Interventions, with CC Score 0-1	1	385.67	NHS reference cost 19/20, JA12L
Breast Cancer MDT Meetings	1	103.13	NHS reference cost 19/20, CMDT_B
Surgery based on the generated HRG code			
Unilateral Excision of Breast with Immediate Pedicled Myocutaneous Flap Reconstruction	0.35	6352	NHS reference cost 19/20, JA32Z
Unilateral Major Breast Procedures with Lymph Node Clearance, with CC Score 5+	0.65	3877	NHS reference cost 19/20, JA38A
Unilateral Delayed Free Perforator Flap Breast Reconstruction	1	12342.04	NHS reference cost 19/20, JA34Z
Endocrine therapy	**Daily use**	**NHS price**	**Source**
Tamoxifen tablet 20 mg once daily (30 tablets)	1	9.01	November BNF 2021, Drug Tariff
Arimidex (anastrozole) tablet 1 mg once daily (28 tablets)	1	68.56	November BNF 2021, Drug Tariff
Aromasine (c) tablet 25 mg once daily (30 tablets)	1	88.80	November BNF 2021, Drug Tariff
Femara (Letrozole) tablet 2.5 mg once daily (28 tablets)	1	90.92	November BNF 2021, Drug Tariff

Note: HRG: Healthcare Resource Groups; NHS: National Health Service; BNF: British National Formula

5.3.6 Data analysis

If relevant, a deterministic base-case analysis was conducted to calculate the incremental cost, life-years (LY) gained, QALYs gained, and the incremental cost-effectiveness ratio (ICER). ICER is an outcome measure for economic evaluations recommended by the NICE guidance in the UK to represent the economic value of an intervention compared with an alternative [133], which is derived from dividing the incremental cost by the incremental QALYs (Section 2.2.4, page 67). INMB (formula in Section 2.2.4, Table 2.7) were also calculated assuming a cost-effectiveness (CE) threshold of £20,000 and £30,000 per QALY gained [304, 305]. According to the NICE guidance, the CE threshold of £20,000 and £30,000 per QALY gained was used in the analysis to present expected net monetary or health benefits [133]. A half-cycle correction was conducted in base case analysis to check the Markov model assumption that each cycle in the analysis is an equal discrete length of time.

A one-way sensitivity analysis investigated how uncertainty in the input parameter values affected the INMB. One-way sensitivity analysis is the most straightforward approach because only one parameter is changed simultaneously, and correlations between parameters are not considered [306]. The results of one-way sensitivity analysis allow a reviewer to assess whether the changes of specific input parameters will impact the output results of economic evaluation, referred to as assessing the robustness of the result to that parameter [306]. Transition probabilities and utility values were varied to the upper and lower values of their 95% confidence intervals. Unit costs varied ± 25% from their base case value (Table 5.3). The results of the one-way sensitivity analysis were presented by a tornado diagram, which shows how sensitive the INMB of surgery versus PET is to the change in the input parameter values [133].

A probabilistic sensitivity analysis (PSA) propagated uncertainty through all input parameters simultaneously via Monte Carlo simulation (10,000 iterations) [307].

Appropriate probability distributions were assigned to each input parameter (Table 5.3). The results were presented graphically using a CE plane, representing the differences in costs and health outcomes between treatment alternatives in two dimensions [160].

The value of information (VOI) analysis was conducted to quantify the expected value of research in reducing decision uncertainty to inform whether a decision can be made based on existing evidence. The PSA outputs were used to calculate the Expected Value of Perfect Information (EVPI) at the patient and population levels at the CE threshold of £20,000. The EVPI per patient is the difference between the expected NMB based on perfect information generated from PSA simulations and the expected NMB based on current information [308, 309] (Formula 5.1) (definition of NMB in Chapter 2, Section 2.2.4).

$$\boldsymbol{EVPI_{patient} = \left[E_{\theta} \max_{j} NMB(j,\theta)\right] - \left[\max_{j} E_{\theta} NMB(j,\theta)\right]} \quad \textbf{(5.1)}$$

The perfect information is meant that there would be no parameter uncertainty, and they would recommend the alternative with the highest NMB in each PSA simulation, presented using the formula (mean value of the maximum between two alternatives in each simulation $\left[E_{\theta} \max_{j} NMB(j,\theta)\right]$). The current information is meant that the alternative that had the greatest expected NMB based on current information presented using the formula (mean value of the net benefit values for all simulations by two alternatives $\left[\max_{j} E_{\theta} NMB(j,\theta)\right]$. Where j is the different alternatives and θ is the values taken by a set of uncertain input parameters.

Population EVPI was calculated over a range of time horizons with discounted at 3.5% per year, assuming a CE threshold of £20,000 per QALY gained. Based on the patient-

level EVPI, population EVPI is calculated according to two elements. First, the annual incidence (n=13,396) of operable older women aged 70+ years with early-stage breast cancer who are fit for surgery was identified from the national audit published in 2022 [11]. Second, the anticipated lifecycle for treatment was uncertain and assumed to be up to ten years. The population size that will benefit from further research (n=115,309) was used to estimate population EVPI [11].

A value of implementation analysis quantifies the value of improving the uptake of surgery in this population of patients [178]. The expected value of perfect implementation (EVPIM) was the difference between the NMB when surgery is implemented perfectly (100% uptake) and when surgery is based on current levels of (imperfect) implementation of alternatives (Formula 5.2), where the ρ_j is the level of implementation for different alternatives,), where $0 \leqslant \rho_j \leqslant 1$ and $\sum_{j=1}^{J} \rho_j = 1$.

$$\mathbf{EVPIM} = \left[\max_{j} \boldsymbol{E_\theta NB(j,\theta)}\right] - \left[\sum \boldsymbol{\rho_j}\, \boldsymbol{E_\theta NB(j,\theta)}\right] \quad \textbf{(5.2)}$$

When expressed in monetary units, the EVPIM provides the upper bound on the cost of implementation strategies to increase uptake. When expressed in health units, the EVPIM provides the net health loss associated with the imperfect uptake of interventions. The current proportions of surgery and PET implemented in routine clinical practice were estimated from the national audit of breast cancer in older patients 2022 who are fit for surgery (surgery 76% of older women; PET: 24% of older women) [11]. Per patient, estimates were scaled to the population level (n=115,309) as EVPI [11]. The population EVPIM was calculated for a cost-effectiveness threshold of £20,000 per QALY gained. Sensitivity analysis of the implementation analysis value was performed by varying ± 10% of surgery proportion.

Table 5.3. Input parameters for the Markov model

Parameters	Deterministic analysis		Probabilistic analysis		Data source
	Value	Range (95% CI)	Distribution	Parameters	
Transition probabilities					
Surgery					
From disease-free to death	Gompertz shape: -2.65 scale: 0.16	shape (-2.98, -2.32) scale (0.11, 0.21)	Multivariate normal	shape: 0.1693 scale: -0.0203 cov: 0.0123	[99]
From disease-free to progressed disease	Gompertz shape: -2.59 scale: -0.14	shape (-3.04, -2.13) scale (-0.22, -0.05)	Multivariate normal	shape: 0.2308 scale: -0.03388 cov: 0.02715	[99]
PET					
From disease-free to death	Log-logistic shape: 1.72 scale: 0.41	shape (1.60, 1.85) scale (0.37, 0.49)	Multivariate normal	shape: 0.0628 scale: -0.0028 cov: 0.07385	[99]
From disease-free to progressed disease	Log-normal shape: 0.98 location: 1.39	shape (0.79, 1.22) location (1.21, 1.61)	Multivariate normal	shape: 0.1251 location: 0.0079 cov:0.07135	[99]
From progressed to death	0.04	(0.035, 0.045)	Beta (α, β)	280, 6610	[298]
From metastasis to death	0.10	(0.085,0.120)	Beta (α, β)	739.5, 6150	[298]
The proportion of patients receiving surgery in the metastasis state	0.42	Fix value	Beta (α, β)	27, 42	[99]
The proportion of patients receiving PET in the metastasis state	0.35	Fix value	Beta (α, β)	27, 39	[99]
Utility					
The stable state of surgery and PET					
Baseline value	0.75	(0.72, 0.79)	Beta (α, β)	191, 63	[272]
Progressed state of surgery and PET					

Parameters	Deterministic analysis		Probabilistic analysis		Data source
	Value	Range (95% CI)	Distribution	Parameters	
Decrements	-0.143	(-0.174, -0.112)	Normal (Mean, SE)	-0.143, 0.016	[239]
Metastatic state of surgery and PET					
Decrements	-0.338	(-0.373, -0.303)	Normal (Mean, SE)	-0.338, 0.000685	[239]
Age decrement (annual)	-0.0013	-0.004, 0.002	Normal (Mean, SE)	-0.0013, 0.001	Chapter 4
Cost					
Surgery	£9342.10				
Mastectomy	£6547.64	Fixed value			[301], [303]
Proportion of mastectomy	35%	(28%-43%)	Beta (α, β)	16340, 30345	[10]
Delayed breast reconstruction of mastectomy	£12722.17	Fixed value			[301], [303]
Breast-conserving surgery	£3996.41	Fixed value			[301], [303]
The proportion of breast-conserving surgery	65%	1- %mastectomy			[10]
Cost of hospital stays for surgery per cycle	£937.00	Fixed value			[10], [301], [303]
Cost of Tamoxifen (per tablet)	£0.31	Fixed value			[300], [303]
Cost of Letrozole (per tablet)	£3.12	Fixed value			[300], [303]
Cost of follow-up for both arms per cycle	£64.43	Fixed value			[301], [303]
Cost of progressed disease	£8251.75	(£5691.10-£11248.21)	Gamma (α, β)	33.88, 487.09	[302], [303]
Cost of metastatic disease	£6223.54	(£4990.12-£7638.91)	Gamma (α, β)	84.83, 146.73	[302], [303]

(Note) The distributions to deterministic analysis were identified by matching the best-fit survival functions;

Values for the multivariate normal distribution obtained from the Cholesky decomposition of the variance-covariance matrix, which was estimated using the distribution to the deterministic analysis;

Abbreviations cov: covariance SE: standard error; CI: confident interval.

5.4 Results

5.4.1 Deterministic base-case analysis

PET is not a cost-effective strategy compared with surgery at the cost-effectiveness threshold of £20,000 to £30,000 for treating older women with operable early-stage breast cancer. The total lifetime cost of PET (£58,288.32) was higher than that of surgery (£30,828.81). PET had an incremental cost of £27,459.51 compared with surgery. The total lifetime QALYs from surgery and PET were 3.59 and 3.75. PET had an incremental QALYs gain of 0.16 compared with PET. The INMB of PET compared with surgery was minus £24,292.25 and minus £22,708.61 at the CE threshold of £20,000 and £30,000, respectively (Table 5.4). The result of the half-cycle correction was reported in Table 5.4, which indicated that surgery is a cost-effective strategy.

Table 5.4. Results of base-case deterministic analysis

Results		**Surgery**	**PET**
Expected cost (£)		£30,828.81	£58,288.32
Life year gained		6.74	8.34
Expected QALYs		3.59	3.75
Incremental cost (£)		-	£27,459.51
Incremental QALYs		-	0.16
ICER		-	£173,395.82 per QALY gain
Net monetary benefit (£)	λ=20000	£41,018.11	£16,725.86
	λ=30000	£76,941.56	£54,232.95
Incremental net monetary benefit (£)	λ=20000		-£24,292.25
	λ=30000		-£22,708.61
Half cycle correction		**Surgery**	**PET**
Expected cost (£)		£26,157.75	£57,838.85
Life year gained		6.49	8.09
Expected QALYs		3.43	3.58
Incremental cost (£)		-	£31,681.10
Incremental QALYs		-	0.16
ICER		-	£202,473.41 per QALY gain
Net monetary benefit (£)	λ=20000	£42,391.84	£13,840.15
	λ=30000	£76,666.64	£49,679.65
Incremental net monetary benefit (£)	λ=20000		-£28,551.69
	λ=30000		-£26,986.99

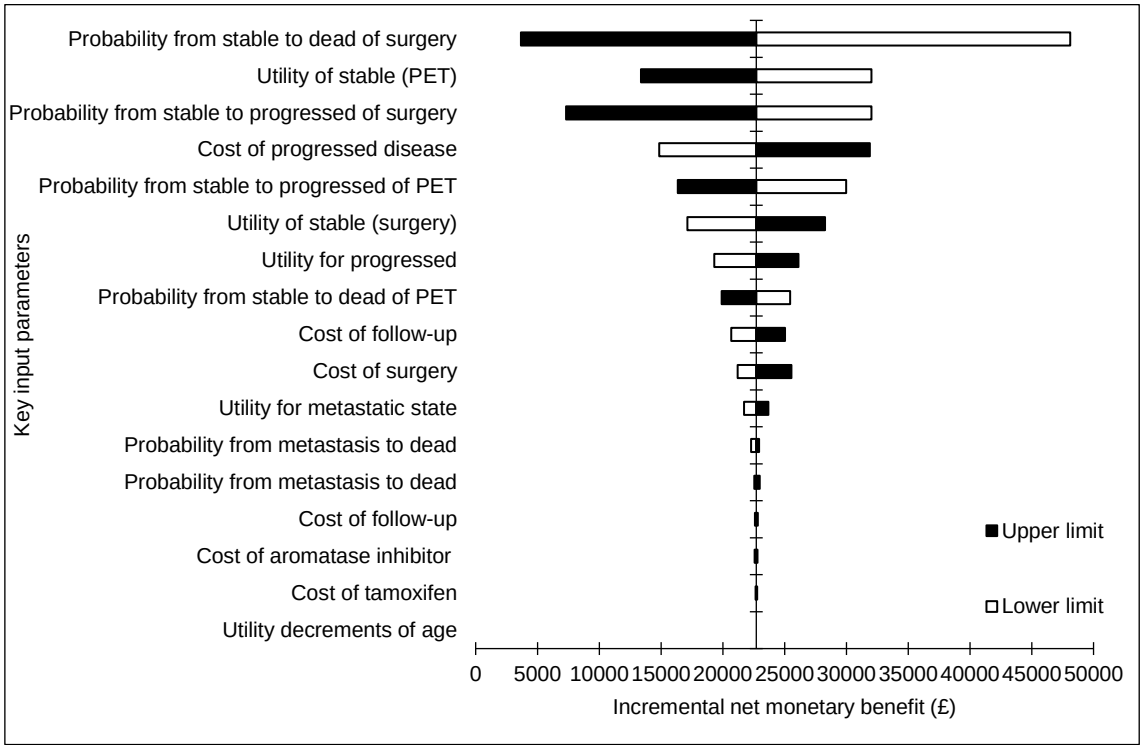
(Note) QALY: quality-adjusted life-years; ICER: incremental cost-effectiveness ratio. PET: Primary endocrine therapy; Incremental values calculated by comparing surgery with PET.

5.4.2 Sensitivity analyses

The one-way sensitivity analyses, reported in the Tornado diagram (Figure 5.2), indicated that the INMB is most sensitive to the parameter uncertainty associated with the transition probabilities from the stable to dead states. The positive results of INMB

for all the parameters suggested that decision-making that PET is not cost-effective will not change despite existing uncertainty. The results are robust to changes in the input parameter values.

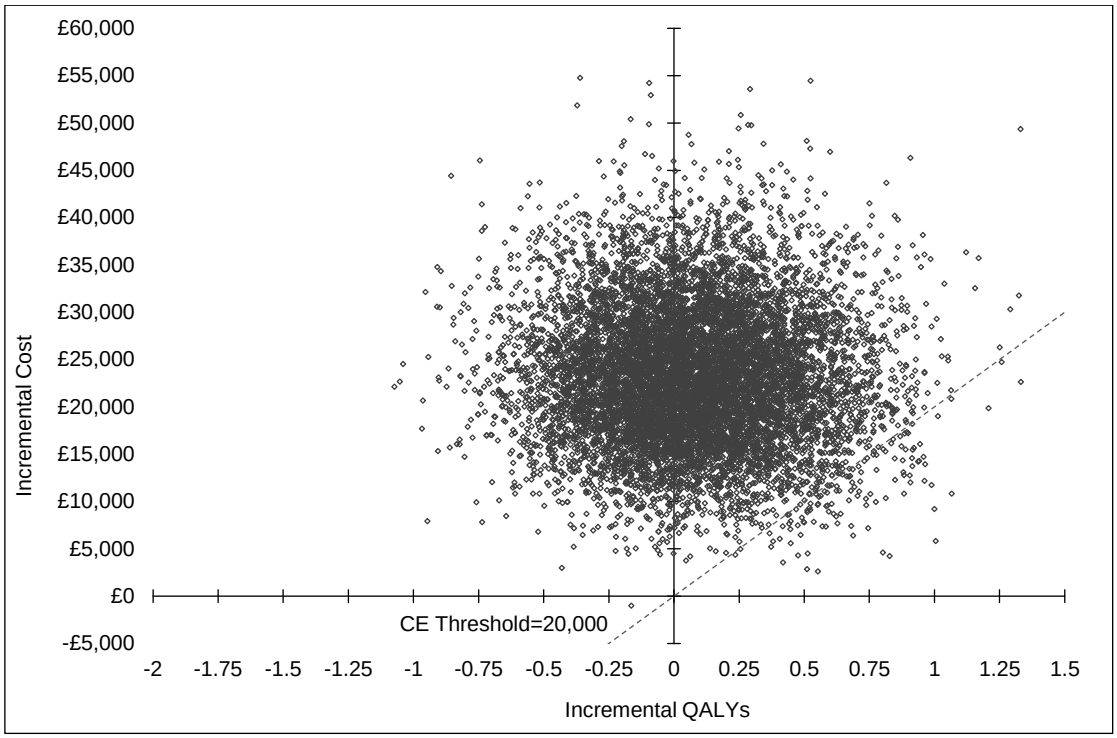
Figure 5.2. Tornado diagram of deterministic sensitivity analysis



(Note) PET: primary endocrine therapy

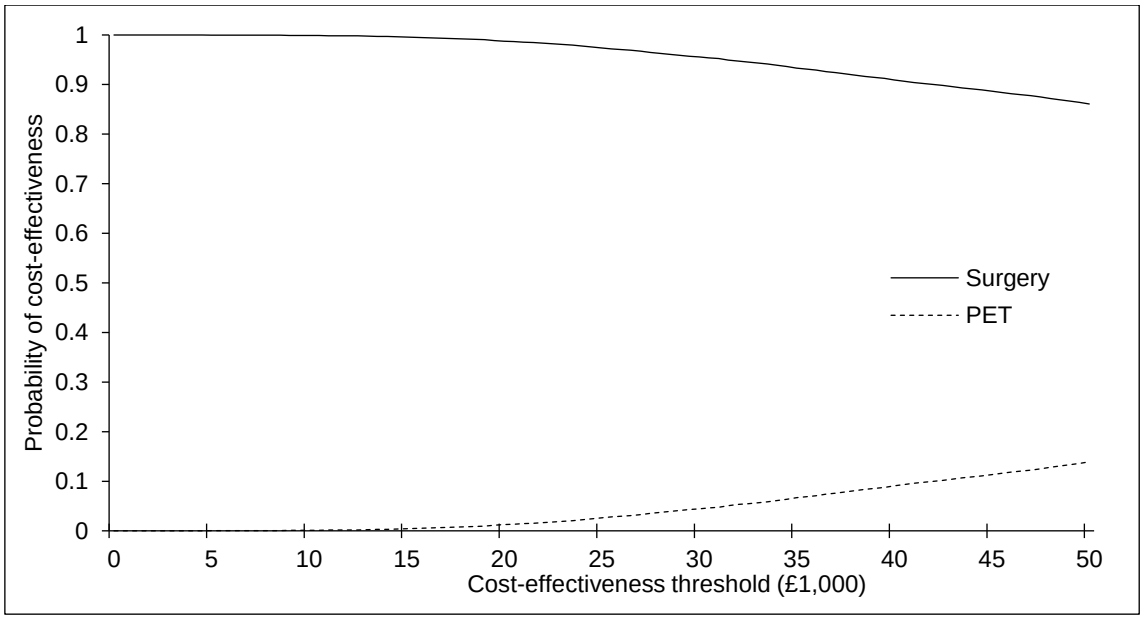
The PSA results indicated that PET is not a cost-effective strategy under certain distributions for each input parameter (Figure 5.3). Most of the points from PSA were located in the north quadrant and upper the cost-effectiveness threshold in the cost-effectiveness plane, illustrating that PET is not a cost-effective strategy with increased costs but decreased QALY gains. According to the CEAC, at a cost-effectiveness threshold of £20,000 per QALY gained, the probability that PET is cost-effective was 1.3%, and when the cost-effectiveness threshold rises to £30,000 per QALY, the probability that PET is cost-effective was 4.4% (Figure 5.4). Therefore, by PSA under certain distributions for each input parameter, PET is not a cost-effective strategy for older patients who are fit for surgery.

Figure 5.3. Cost-effectiveness plane of the probabilistic sensitivity analysis



(Note) PET against surgery, QALY: quality-adjusted life-year; CE: cost-effectiveness

Figure 5.4. Cost-effectiveness acceptability curve

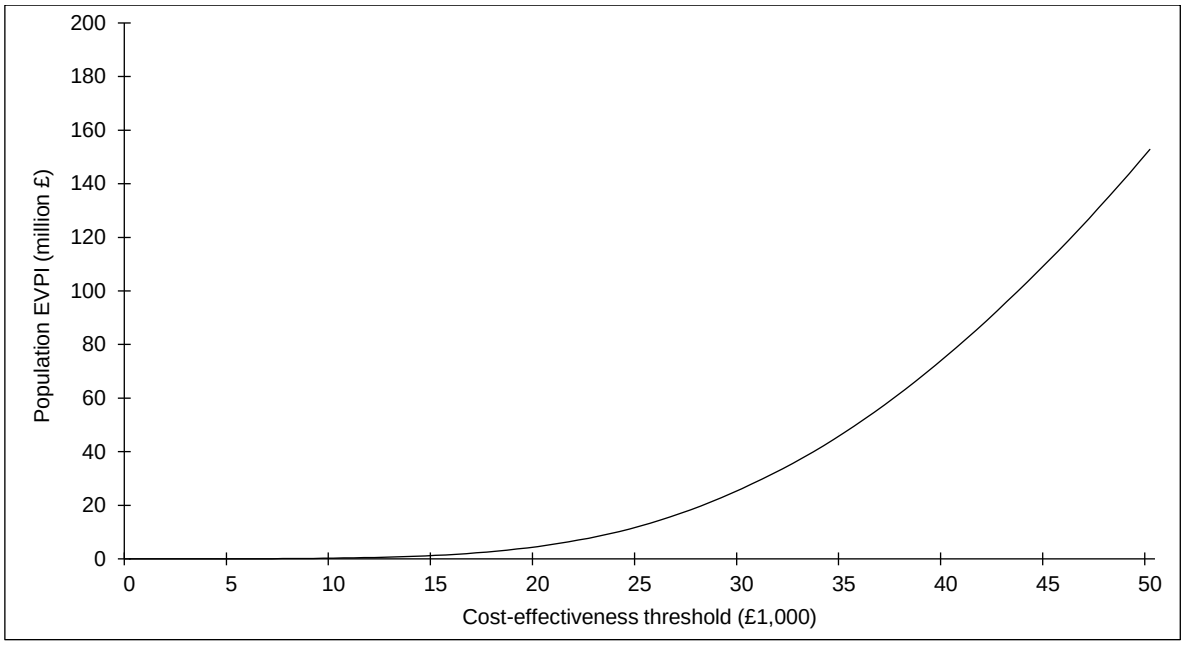


(Note) PET: Primary endocrine therapy

5.4.3 Value of information analysis

The EVPI per patient was £39.87 at the cost-effective threshold of £20,000. When scaled to the population level, the population EVPI were £4,597,644.62 (Figure 5.5) and rose continuously.

Figure 5.5. Population expected value of perfect information



(Note): EVPI: the expected value of perfect information.

5.4.4 Value of implementation analysis

The imperfect implementation of surgery resulted in a loss of 0.29 QALYs and £5,830.14 expressed by NMB per patient at a CE threshold of £20,000 per QALY gained. When scaling this to the population level (n=115,309), imperfect surgery implementation will result in a net loss of 33,613.25 QALYs or £672,264,959.26 (0.67 billion) over the coming ten years.

By the sensitivity analysis of changing proportions of surgery, there was a loss between 0.17 (86% of surgery) and 0.41 (66% of surgery) QALYs per patient, or between

£3,400.91 and £8,259.36 NMB. When scaled to the population level, the loss was between 19,607.73 and 47,618.77 QALYs or between £0.39 and £0.95 billion NMB.

5.5 Discussion

This study quantified the health and economic loss of PET versus surgery in operable older women with early-stage breast cancer to strengthen current guidelines for early-stage breast cancer. PET is not a cost-effective strategy for older women with early-stage breast cancer with the operable disease, which aligns with the previous CEA by Holmes *et al.* (2021) [180]. Hence, Increasing the surgery uptake rate for operable older patients in routine practice improves population health and healthcare resource use.

The quantified health loss of PET for operable older patients can inform clinicians, patients and policymakers to make an evidence-based decision on breast cancer treatment. Clinicians should provide an evidence-based clinical recommendation, although the benefits and risks of treatments should be provided to patients in line with patient preferences, goals and circumstances [310]. Clinical effectiveness is essential evidence when deciding on treatment choices. Also, cost-effectiveness is another essential evidence to provide the most appropriate treatment under the limited healthcare resource. This study found that the health loss of applying PET in older women with operable early-stage breast cancer is 0.29 QALY per patient and £8,733.40 NMB, which can provide evidence for patients to make a trade-off between treatments. Moreover, the estimated health loss of PET at the population level is 33,613.25 QALYs (NMB of £0.67 billion) to inform policy decision-making that surgery should be encouraged as the first-line treatment, irrespective of age if patients are physically fit for surgery.

After a pragmatic search of the literature, only one published economic evaluation by Holmes *et al.* (2021) was identified that compared surgery with non-surgical treatment

[180], and the remaining economic evaluations all compared the cost-effectiveness of different post-surgical adjuvant treatments. In line with the previously published economic evaluations, Holmes *et al*. (2021) found that surgery is a cost-effective strategy for older women aged ≥70 years with early-stage breast cancer who have no co-morbidities [180]. Furthermore, PET was a cost-effective initial treatment strategy for older women with early-stage breast cancer over 90 years with a higher burden of co-morbidities [180].

The critical difference between the CEA in Chapter 5 and Holmes *et al.* (2022) was the approach and data source used to estimate the clinical effectiveness of surgery and PET. Holmes *et al.* estimated the probabilities of death from stable and progression for surgery from an RCT. They calculated the probabilities of PET using a hazard ratio (i.e., a constant ratio) between surgery and PET extracted from a meta-analysis [94]. Compared with Holmes *et al.*'s approach assuming the time-varying consistent hazard ratio between two treatments, the CEA in Chapter 5 was advantageous because the probabilities of surgery and PET were estimated from an RCT, which reported the survival curves of surgery and PET. Hence, the time-varying probabilities of surgery and PET was independently estimated from survival functions, i.e., the survival functions of overall survivals and progression survivals fit the Gompertz distribution for surgery and PET, and Logistic and Log-normal distributions for surgery and PET, respectively. Re-building survival curves is a better, less biased approach to estimating the clinical effectiveness of interventions and comparator changing with time because the magnitude of treatment effects between two strategies is unlikely consistent with time.

However, the cost-effectiveness of PET may vary in different patient groups. According to the European Society of Breast Cancer Specialists (EUSOMA) and the International Society of Geriatric Oncology (SIOG), PET is recommended for women with breast cancer, short life expectancy and high ER-positive status [311]. Surgery is still the main

first-line treatment strategy in routine clinical practice. A proportion of older patients are not feasible for surgery through the pre-operative assessment. The pre-operative assessment assesses whether the patient's physical functioning (for example, frailty, disability and co-morbidity) can tolerate surgery to judge the surgery's feasibility [312].

Therefore, PET may still be cost-effective for a certain subgroup of patients, of which frailty may be crucial in predicting the cost-effectiveness of PET in older women with early-stage breast cancer in economic evaluations (Chapter 7). There is a lack of evidence in terms of the clinical and comparative effectiveness of PET versus surgery in older women with early-stage breast cancer who are unfit for surgery because patients with higher frailty or multiple co-morbidities were often excluded from RCTs due to a higher risk of mortality [106, 107].

Real-world data is a feasible data source to estimate clinical and comparative effectiveness for economic evaluation. Still, analysts will need to control for confounding, for example, selection bias [313]. Therefore, the primary care records (Clinical Practice Research Datalink [314, 315]) linked with cancer diagnosis characteristics (the National Cancer Registration Analysis Service [232]), secondary care data (Hospital Episode Statistics [316]) and death information (Office for National Statistics Death Registration [317]) as a feasible data sources were used to design an observational study to inform the treatment effects in older women with early-stage breast cancer stratified by frailty and comorbidity (Chapter 6).

There are some limitations to this study. Undoubtedly, uncertainty is inherent in this economic evaluation, and three types of uncertainty in an economic evaluation can be managed through a specific process (Section 2.2.5). First, for the methodology uncertainty, model-based economic evaluation is the NICE guidance recommended methodology to assess the decision problems for health technologies, and the rationale

for the modelling development should be provided [125]. According to the results of Chapter 3, a systematic review of the economic evaluation for breast cancer, three states the Markov model is the most common modelling for assessing the lifelong cost-effectiveness of breast cancer treatment strategies [15]. Hence, despite some methodology uncertainty, the impacts on the results can be tolerated.

Second, for the parameter uncertainty, there was a concern that this CEA might underestimate the uncertainty by using a single RCT to estimate the clinical effects, despite applying the probabilistic sensitivity analysis to assess the parameter uncertainty. According to the NICE, relying on a single study as the primary data source of effectiveness is not a good practice for decision modelling due to underestimating the uncertainty; instead, using the systematic review or meta-analysis to assess the treatment effects comprehensively is recommended [13]. However, a key advantage of using these RCT data is the availability of lifetime outcomes which are typically not included in evidence synthesis of short-term treatment effects. Also, selecting treatment choices in the RCT conducted a decade ago might not entirely reflect the current practice. Favourably, although the modelling parameters were estimated from a single RCT in this CEA, the RCT's result of treatment effects for PET compared with surgery was consistent with the Cochrane review by Morgan et al. (2017) [94].

In addition, there are some limitations in the study design of this RCT. First, this RCT did not identify the ER status of the recruited participants, and this may underestimate the effects of PET. Second, this surgery alone was not used as a routine clinical practice for ER+ breast cancer but used surgery plus adjuvant ET. This RCT underestimated the effectiveness of surgery strategy in current clinical practice. Third, surgery type was improved in these 20 years, and mastectomy wedge was not adopted as the procedure but breast-conserving surgery, which enhanced the post-surgical quality of life. In summary, considering these limitations of RCT for the analysis, the clinical effectiveness

of surgery (surgery strategy in current practice means surgery plus adjuvant ET) was underestimated. This Chapter provided the cost-effectiveness of PET compared with surgery as a lower-bound, which can be used as evidence to strengthen the current NICE recommendations for early-stage breast cancer.

Finally, there is some structural uncertainty in this model-based economic evaluation which is reported in the following. First, the value of increasing the uptake of surgery in this population will be underestimated. According to the clinical guidelines, patients with early-stage breast cancer are unlikely to receive surgery alone in routine practice; instead, post-surgical adjuvant therapies (for example, chemotherapy, radiotherapy, endocrine therapy, or biological therapy) are likely to be used [3] as they can improve survival [318, 319]. Therefore, the results of this study estimate the lower bound of the loss from the imperfect implementation of surgery.

Second, this study did not include the probability and related cost of side effects induced by treatment (for example, post-surgical lymphedema or osteoporosis induced by PET). Nonetheless, three state model structure was in line with the previous economic evaluation by Holmes *et al.* [199], in which the model included the side effects of surgery and PET and refined stratification of surgical procedure types (i.e., mastectomy or BCS) by age strata. The results that PET is not a cost-effective strategy in this chapter were in line with the NICE guideline recommendation and previous economic evaluations by Holmes *et al.* [199], and there would be no value in conducting more research by the EVPI analysis (£0).

Also, there are some advantages of this study. First, this CEA used RCT with a 20-year follow-up duration as the data source to estimate the clinical effects of surgery and PET to provide reliable results to inform the decision-making of clinicians, patients, and policymakers. Second, this is the first time that the value of imperfect implementation for

surgery was quantified in England. This evidence will inform clinicians and policymakers to strengthen the uptake of surgery as the first-line treatment for operable patients according to the current clinical guideline to improve health resource allocation and population health outcomes.

5.6 Conclusion

The findings of this study indicated that PET is not a relatively cost-effective strategy compared to surgery for older patients who are physically fit for surgery, which strengthens current national guidelines for managing breast cancer in older women based on good-quality trial data for operable patients. However, there is still a lack of data to generate economic evidence for older patients with early-stage breast cancer who are unfit for surgery due to frailty or comorbidity. As discussed in Chapter 2, there is a challenge in conducting RCT to evaluate the clinical effectiveness or efficacy of PET and surgery in frail older patients. Therefore, an observational study was conducted in Chapter 6 to estimate the treatment effects on frail patients to inform further economic evaluation (Chapter 7).

Chapter 6 Comparative survival of early-stage breast cancer in postmenopausal women receiving surgery versus primary endocrine therapy

Chapter 6 reports a matched cohort study with two analytical sets to evaluate (1) the survival consequences for the patients with breast cancer diagnosis compared to the population without cancer diagnosis; (2) the survival consequences of PET and surgery for the cohort with breast cancer diagnosis stratified by levels of frailty and comorbidity. This chapter reports following the structure with an introduction (Section 6.1), aim and objectives (Section 6.2), methods (Section 6.3), results (Section 6.4), discussion (Section 6.5) and conclusion (Section 6.6).

6.1 Introduction

PET has been suggested to be given to patients with ER+ breast cancer who are unfit for surgery due to impaired physical functioning from the SIOG and EUSOMA [12]. Physical functioning is the key influential factor in selecting the treatment of early-stage breast cancer, and many studies indicated that older age is highly associated with impaired physical functioning. In addition, there is a higher proportion of ER+ in older women aged ≥ 70 years compared to their younger counterparts aged <70. Consequently, older women with early-stage breast cancer are more likely to receive PET than their younger counterparts. Indeed, the proportion of PET used in older women with breast cancer increased, according to the national audit of breast cancer in older women [11] (Chapter 2).

Two previously published systematic reviews of randomised control trials and observational studies assessed PET's clinical and comparative effectiveness compared with surgery [94, 111] (reports in Chapter 2). One systematic review of RCTs results indicated no statistical difference in overall survival between surgery and PET [94]. However, the recruited participants in RCTs were limited to older women with early-stage

breast cancer who were fit for surgery [94]. In another systematic review, the results of cohort studies cannot be synthesised due to the variation in follow-up duration [111], and the selection bias existed as patients receiving PET were older ages and had weak physical functioning (frail or comorbidity) [111].

Moreover, patients with multi-morbidity or frailty are often excluded from RCTs due to the risk of potential treatment-related adverse consequences [106, 107]. Currently, the only RCT that assessed the clinical efficacy of PET versus surgery in older women with early-stage breast cancer stratified by health status failed to recruit sufficient participants [108]. Some observational studies in older women with breast cancer and impaired physical functioning found the overall survival in patients receiving surgery was superior to those who received PET [113-118]. However, the confounding by indication remains intractable.

A prospective multiple-centre cohort study was conducted in the UK to determine factors influencing treatment selection and clinical outcomes of surgery for older patients with breast cancer [290]. Of the 3375 older women (median age: 76, range: 70 to 95) recruited in this study, 83.4% received surgery. In the study, patient characteristics of frailty, comorbidity, and obesity were evaluated for the association with surgery status (i.e., different surgery types; or whether they receive surgery or not), in which the frailty, comorbidity and obesity were measured by Instrumental Activities of Daily Living (IADL), Charlson Comorbidity Index (CCI), and Body Mass Index (BMI). IADL is a score measuring the independent lifestyle ranging from 0 to 100, and the higher the score, the better the physical functioning. The results indicated that younger age (OR: 0.91; 95%CI: 0.87, 0.96), better physical functioning (OR: 1.26; 95%CI: 1.06, 1.49) and lower co-morbidity index (OR: 0.75; 95%CI: 0.63, 0.88) significantly predicted surgical treatments [290].

However, according to the previous discussion (Chapter 2, Section 2.1.5), using RCTs is challenging to evaluate the clinical and comparative effectiveness of PET versus surgery for older patients unfit for surgery due to frailty or comorbidity. Also, previous observational studies did not well-controlled selection bias between PET and surgery in routine clinical practice. Therefore, there still is a lack of high-quality clinical evidence to indicate PET's clinical and comparative clinical effectiveness against surgery in older women with early-stage breast cancer who are unfit for surgery due to frailty or comorbidity.

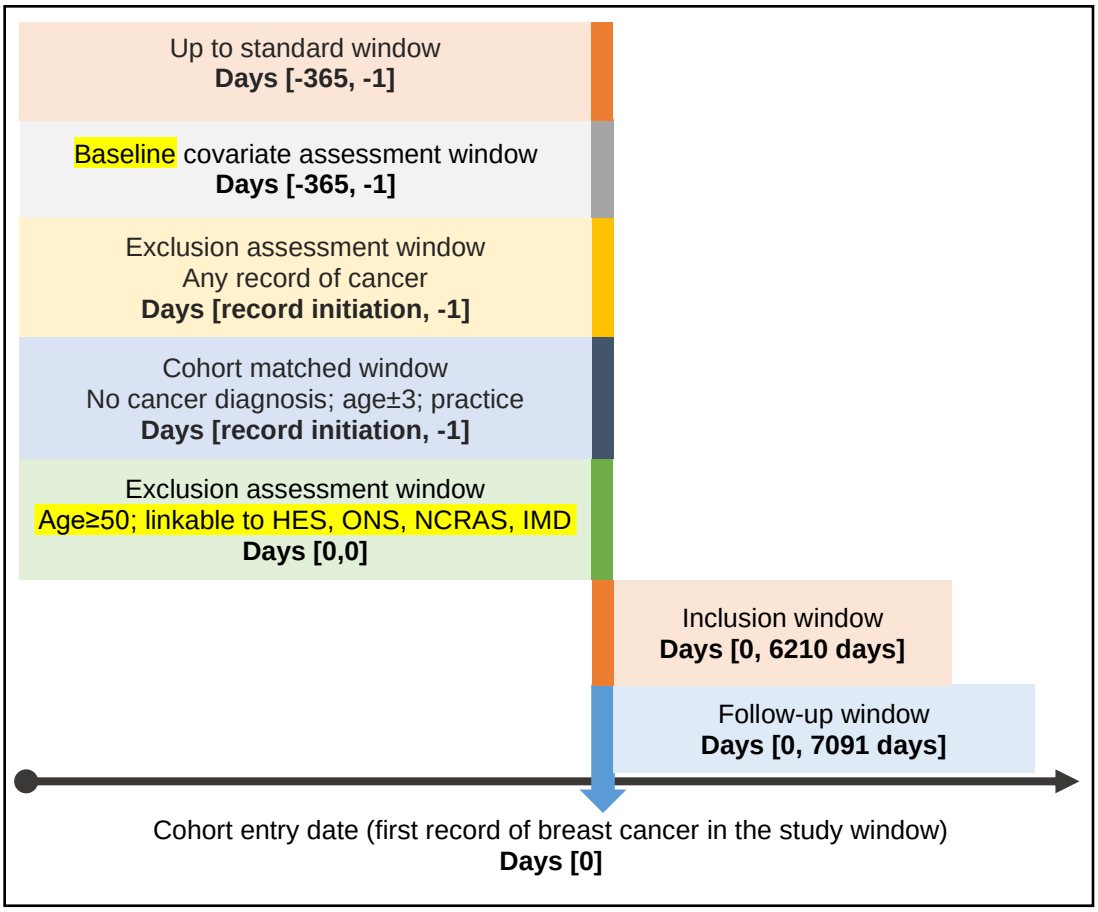
6.2 Aim and objectives

Chapter 6 reports a matched cohort study with two analytical sets to progressively investigate the impacts of age and the level of frailty on the clinical outcomes of female breast cancer. A graphical depiction of the studies is presented in Figure 6.1.

First, to validate whether the age of 70-year is an appropriate cut-off age for older women, a matched cohort study to compare the non-cancer cohort with the breast cancer cohort was conducted by matching postmenopausal women (defined age ≥ 50 years) with early-stage breast cancer (study cohort) to those without a cancer diagnosis (matched cohort) in different age groups (i.e., younger age: 50 to 69 years; older age: ≥ 70 years). For the analysis of the non-cancer cohort vs the cancer cohort, (1) the overall survivals were compared between the non-cancer cohort vs the cancer cohort; (2) the overall survivals were further compared between the non-cancer cohort and breast cancer cohort by two initial treatment strategies.

Second, another analysis within the cancer cohort was conducted on older women (≥ 70 years) with early-stage breast cancer to evaluate the overall survival and breast cancer-specific mortality of PET and surgery in older patients stratified by levels of frailty and comorbidity.

Figure 6.1. Diagram of the study design



(Note) SACT: Systemic Anti-Cancer Treatment; RTDS: National Radiotherapy Dataset; HES APC: Hospital Episode Statistics Admitted Patient Care.

6.3 Methods

6.3.1 Data sources

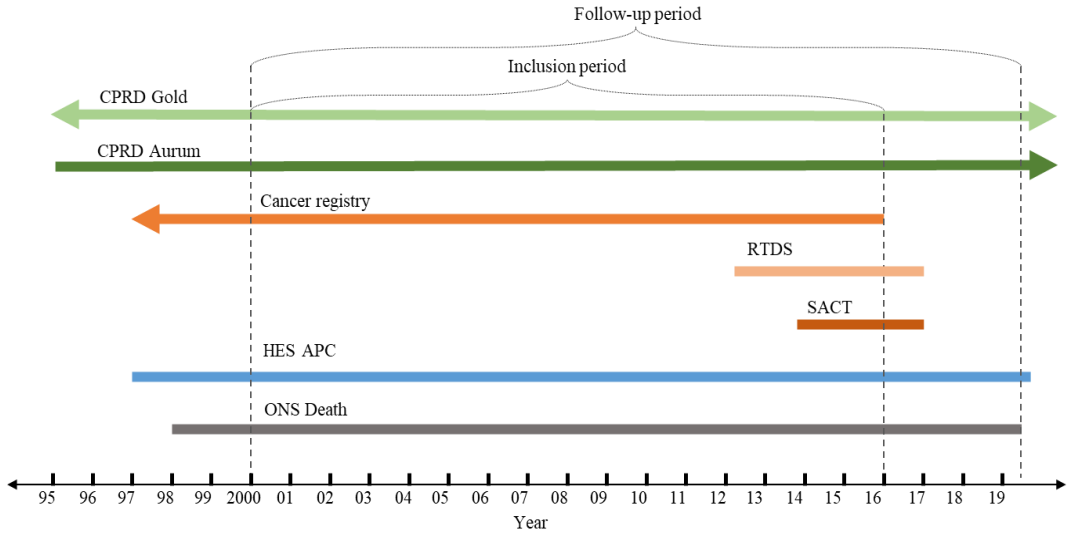
This chapter is part of a matched cohort study that evaluated the long-term outcomes of 20-site cancers compared with those without cancer using the Clinical Practice Research Datalink (CPRD) linking with other healthcare databases in the UK. The study protocol was approved by the Independent Scientific Advisory Committee in April 2020 (20_079R) for accessing the CPRD and linkage databases (ISAC protocol reported in Appendix 15).

The study population of the matched cohort study (of 20-site cancers) was identified using large healthcare databases in England, including the Clinical Practice Research Datalink (CPRD) Gold and Aurum, linked to three national data sources, Hospital

Episode Statistics (HES) Admitted Patient Care (APC), Outpatient (OP) and Accident and Emergency (AE); the Cancer Registrations from the National Cancer Registration and Analysis Service (NCRAS); and the Office for National Statistics (ONS) patient-level Death Registration and Index of Multiple Deprivation (IMD).

The data identified from CPRD, HES, NCRAS and ONS Death registration were extracted and processed by the CPRD team. Public Health England processed the linkage and extraction of NCRAS records. The inclusion period for the study population was based on the most overlapped period among all databases (from 1 January 2000 to 31 December 2016), and the outcome follow-up period ended on 31 May 2019 due to the available period of ONS Death Registration (Figure 6.2). A matched cohort group to the 20 sites cancer patients (including female and male) was selected from people registered in the general practices that consented to CPRD and the linkage to HES, NCRAS, and ONS Death Registration, with no cancer diagnosis, and matched to the study cohort by age (±3 years at the diagnosis age), gender and medical practice on the index date. Each patient in the cancer cohort was matched up to five controls (Figure 6.3).

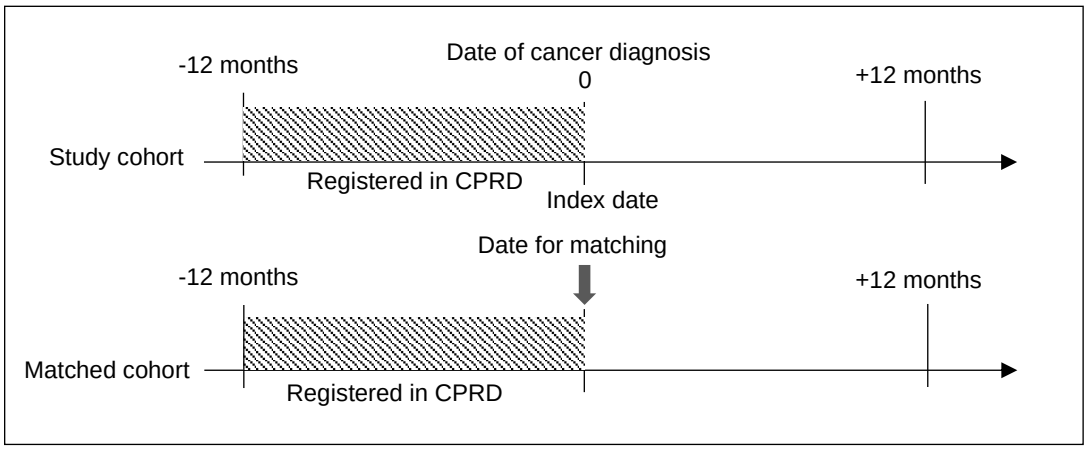
Figure 6.2. Duration of each database used in this study



Source	Dataset	Available duration	Population
National Cancer Registration and Analysis Services (Set 18)	Cancer Registry	January 1990 to December 2016	England
	Systemic Anti-Cancer Treatment	January 2014 to September 2017	England
	National Radiotherapy Dataset	April 2012 to September 2017	England
Clinical Practice Research Datalink (Set 19)	CPRD Gold	1987 to June 2020 (Set 19)	UK
	CPRD Aurum	1995 to June 2020 (Set 19)	England
Hospital Episode Statistics (Set 18)	Admitted Patient Care	April 1997 to June 2019 (Set 18)	England
	Outpatient	April 2003 to June 2019 (Set 18)	England
Office for National Statistics (Set 18)	Death registration	January 1998 to 1 May 2019	England
	Index of Multiple Deprivation	April 2007 to November 2015	England

(Note) SACT: Systemic Anti-Cancer Treatment; RTDS: National Radiotherapy Dataset; HES APC: Hospital Episode Statistics Admitted Patient Care. The available duration was according to the version of set 18 (released in April 2020) and set 19 (released in October 2020).

Figure 6.3. Index date matching for patients with breast cancer



(Note) CPRD: Clinical Practice Research Datalink

CPRD is one of the largest primary care databases in the UK, accounting for nearly 8.3% of the UK population [320]. It includes anonymised information on patients' demographics, diagnoses, consultations, specialist referrals, prescribed medications, and biomedical laboratory tests, longitudinally collected in two datasets, CPRD GOLD and Aurum, according to the two major electronic medical systems (Vision™ and EMIS™) used in general practice (GP). CPRD GOLD and CPRD Aurum differ in record coding and regions of coverage [314, 315]. CPRD can be linked to the relevant HES, NCRAS and ONS databases, which provide critical information for this study.

The HES APC and OP are hospital administrative data for each episode of admissions and outpatient visits at NHS hospitals across England, including episode duration, as well as primary diagnosis and treatment procedures that are recorded by International Classification of Diseases 10th version codes (ICD-10) and OPCS Classification of Interventions and Procedures version 4 codes (OPCS-4), respectively [316].

The NCRAS collects, quality assures, and analyses data on all people living in England diagnosed with malignant and pre-malignant neoplasms, with national coverage since 1971, including the information on the cancer diagnosis recorded by ICD-10 codes,

tumour characteristics, and appropriate treatments. The ONS Death Registration in England collects timely surveillance of mortality in England broken down by sex, age, and the cause of death, and the cause of death is recorded by the ICD-10 code [317]. The ONS Death Registration is the commonly used and validated data source to identify the UK's date and cause of death [321].

6.3.2 Study population

The study cohort was identified from the matched cohort study population, which consisted of postmenopausal women (≥50 years at diagnosis) newly diagnosed with ER+ early breast cancer. The cohort was identified from people registered in the general practices that consented to CPRD linkable to HES, NCRAS, and ONS Death Registration from 1 January 2000 to 31 December 2016; and then followed up from the diagnosis date (index date) to the endpoint, i.e., the date of death, transfer out of practice, or the end of the follow-up, whichever appears first. (the ICD-10 code and Read code of breast cancer diagnosis reported in Appendix 16, Appendix 17, and Appendix 18)

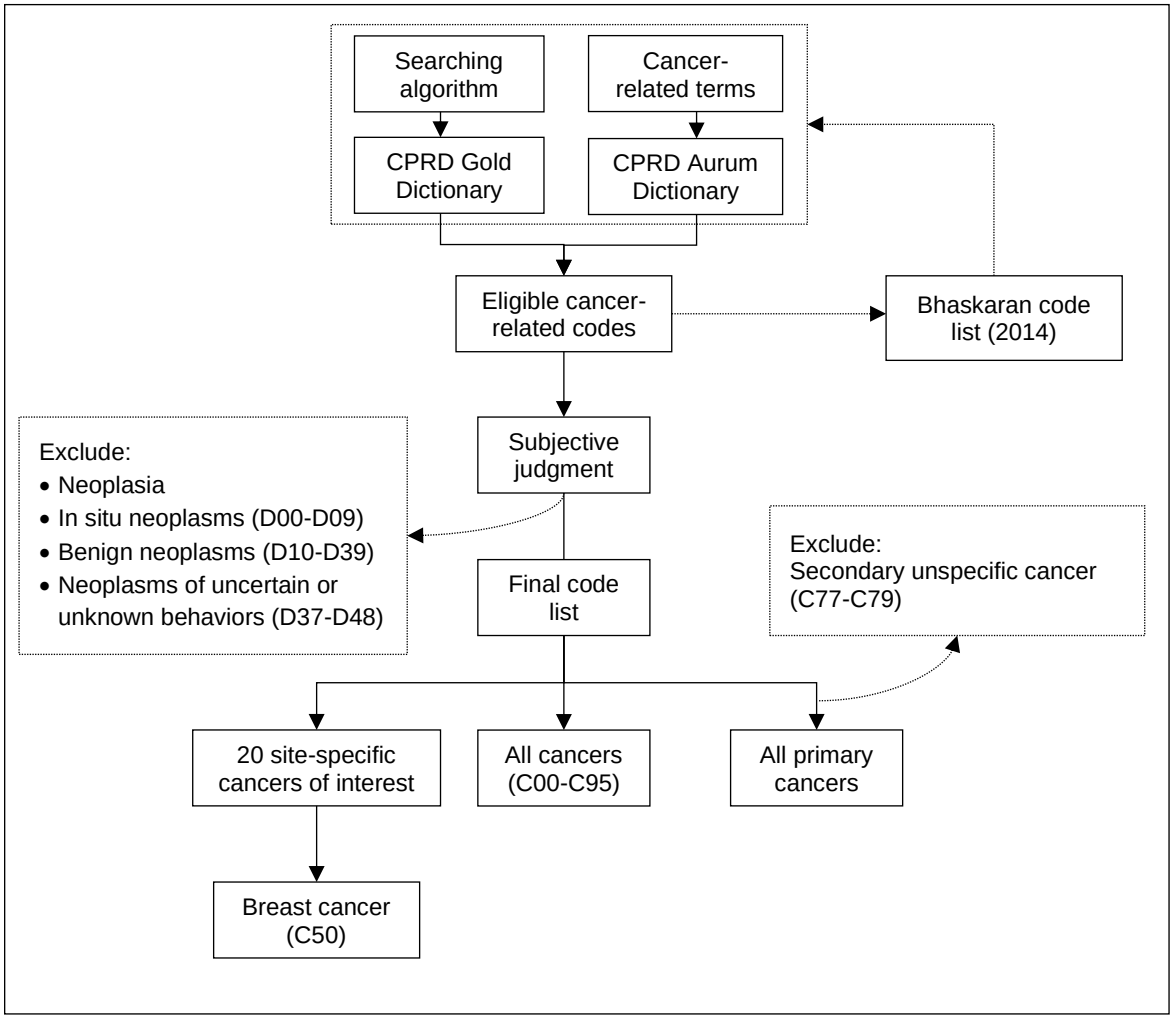
The study cohort fulfilled the following inclusion criteria: (1) female patients having records in CPRD, cancer registry, and HES database; (2) had a record of newly-diagnosed breast cancer, either ICD-10 code (C50) in HES or SNOMED code, in the CPRD during the inclusion period; (3) aged ≥50 years at breast cancer diagnosis; (4) diagnosed with ER-positive primary early-stage breast cancer (stage I, II, and IIIA), all the patients with surgery or endocrine therapy were identified as early-stage breast cancer or ER-positive, respectively; (5) up-to-standard practice data in the CPRD.

The code list of 20 site-specific cancers was developed by referring to published literature [314] and an algorithm generated by the research team (Figure 6.4). The codes for breast cancer diagnosis were applied in this study. The early-stage breast cancer was defined according to the stage (stage I or II) recorded in NCRAS. General practices

in CPRD were classified as 'up to standard' when the practice meets specified minimum quality criteria [232, 314-316].

Furthermore, individuals were excluded if the patient's record had a "Death Certificate Only" flagged in NCRAS cancer registry data, which means breast cancer diagnosis was retrieved from the death certificate; thus, the accurate date of diagnosis was unavailable. Moreover, patients with the same diagnosis and death date were excluded due to no follow-up time available.

Figure 6.4. Procedure for code list development



(Note) Bhaskaran code list (2014) [322]; CPRD: Clinical Practice Research Datalink

A matched cohort group of the thesis was identified from the matched cohort study of 20-site cancers, that is, female breast cancer. The matched group in the thesis were matched to the study cohort by age (±3 years at the diagnosis age) and medical practice on the index date. The study cohort and matched cohort were categorised into younger (50-69 years) and older (⩾70 years) age strata during the follow-up period.

6.3.3 Treatment exposure

The exposure of the matched cohort study was whether the postmenopausal women with a confirmed diagnosis of early-stage breast cancer (receiving surgery/PET as initial treatment) or without a cancer diagnosis. On the other hand, the exposure in the cohort study was the initial treatment, i.e., the first treatment received within 12 months after a breast cancer diagnosis.

The initial treatment was categorised into two groups: (1) surgery with or without adjuvant (or neoadjuvant) treatments (for example, chemotherapy and radiotherapy) or (2) PET. One year was selected as the observational window for surgery in the thesis for two reasons. (1) the Care Quality Commission (CQC) in England recommended that the initial treatment for breast cancer should commence within 62 days [323] (Chapter 2, Section 2.1.1.1). Besides, the NICE guideline recommended an approximately 6-month course of pre-surgical neoadjuvant chemotherapy, radiotherapy, or endocrine therapy [3], and thus surgical procedures should be started within one year. (2) According to expert opinion, one-year was a feasible time window to identify initial surgical procedures.

The initial surgery group included patients who received either breast-conserving surgery (BCS) or mastectomy with or without adjuvant therapy within 12 months after the index date. Patients who did not receive surgery but received endocrine therapy, including tamoxifen or aromatase inhibitors, with or without chemotherapy, radiotherapy, or

biological therapy within a 12-month window, were categorised in the PET group. The patients categorised into the PET group who received surgery (including mastectomy or BCS) after 1-year were excluded from the study cohort because it is unknown whether the patient was diagnosed with primary breast cancer.

The initial treatments were primarily identified from records in NCRAS, supplemented by screening surgical procedures of the Office of Population Censuses and Surveys Classification of Interventions and Procedures version 4 (OPCS-4) codes in HES APC; Read code (product codes) of endocrine therapy in CPRD (Endocrine medication for breast cancer BNF code in Appendix 19). If the surgery date was inconsistent between the NCRAS and HES, then the earliest recorded date was utilised. (The OPCS-4 codes of breast cancer are reported in Appendix 20)

6.3.4 Outcome measure

Overall survival (OS) was the primary outcome for the matched cohort study of two analyses, estimated from all-cause mortality (ACM) events. Also, breast-cancer-specific mortality (BCSM) [324] was measured as a secondary outcome in the cohort study to minimise confounding of other competing risks (for example, ageing, frailty or multi-morbidities). ACM and BCSM events were identified from ONS death registration. BCSM events were identified through the ICD-10 codes (C50.X) on ONS death registration [317]. The follow-up time of death events ended on 31 May 2019 due to the ONS Death Registration data availability.

6.3.5 Covariates

Baseline characteristics that may influence mortality risk, including diagnosis age (on the index date), socioeconomic status, comorbidities, and frailty, were identified on the diagnosis date for the patients with breast cancer and one year before the index date for

the matched cohort as covariates. Although age was used as one variable to match the study cohort and their matches, age was not performed in a matching process for the analysis within the cancer cohort by different initial treatments. Therefore, it is necessary to adjust the influence of age on the initial treatment strategy selection.

Nineteen comorbidities, identified by SNOMED codes in CPRD and ICD-10 codes in HES, were used to calculate the Charlson Comorbidity Index (CCI) using validated algorithms [325]. The calculated CCI was stratified into three levels low (0-2), intermediate (3-4), and high (≥5), based on pre-defined cut-offs by Crooks *et al.* (2016) [325]. Conventionally, the CCI is used to predict the long-term (10 years) ACM for a patient with a range of comorbid conditions [325]. There were nineteen morbidities identified using ICD-10 codes in HES and Read code in the CPRD, and a relative weight for each condition from 1 to 6 to calculate CCI. [325]

Symptoms related to frailty (n=109) identified by screening ICD-10 codes in HES were used to calculate the Hospital Frailty Risk Score (HFRS) [76]. There were 109 symptoms recognised by three-character ICD-10 diagnostic codes identified from the HES APC, and a relative weight for each condition from 0.1 to 7.1 to estimate HFRS [76]. HFRS ranging from 0 to 99 is associated with three short-term outcomes in all hospitalised patients: 30-day mortality, extended hospital stay (> ten days in hospital), and emergency readmission within 30 days of discharge [76]. The estimated HFRS was stratified into three levels according to the external validation data: non-frail (<5), pre-frail (5-14), and frail (⩾15) based on pre-defined cut-offs by Gilbert et al. (2018) because the original results of HFRD were heavy skew to the lower score side [76].

Therefore, two physical functioning-related co-variates were selected in this study to adjust the long-term and short-term confounding. Missing data for the CCI and HFRS were assumed to have no comorbidity or risk of frailty. Furthermore, the socioeconomic

status, i.e., Index of Multiple Deprivation (IMD), recorded as a decile from 0 (most impoverished) to 10 (rich) in ONS data, was grouped into five categories (I: 1-2; II: 3-4; III: 5-6; IV: 7-8; V: 9-10). (the Read and ICD-10 code for CCI reported in Appendix 21 and Appendix 22; the ICD-code for HFRS reported in Appendix 23)

6.3.6 Statistical analysis

Descriptive statistics were used to report the characteristic of patients, exposure, outcome and covariates. Continuous variables were summarised in mean and standard deviation (SD) or median and interquartile range (IQR), while categorical variables were reported in proportions. The Chi-square and Wilcoxon signed-rank tests assessed the statistically significant difference ($P<0.05$) of categorical and continuous variables, respectively.

The propensity score technique was adopted to manage the confounding in this study. Propensity score is a statistical technique used in observational studies to address confounding bias when estimating the causal effect of an exposure or treatment on an outcome. [326]. The propensity score represents the probability or likelihood of an individual receiving a particular treatment or exposure, given their observed characteristics or covariates [326]. The process of calculating the propensity score involves constructing a predictive model, typically using logistic regression, where the treatment/exposure status is the dependent variable and the covariates are the independent variables. The resulting propensity score represents the predicted probability of being in the treatment group based on the covariate values. The following steps describe the detailed procedure of calculating the propensity score.

Step 1: Select appropriate co-variates to calculate the propensity score.

In practice, the propensity score for patients receiving surgery or PET in two age strata (younger and older) was estimated based on four confounders (i.e., age strata with 5-year intervals, three-level HFRS and CCI; five-level IMD [327]) that may lead to different likelihoods of receiving initial treatments for breast cancer [328]. Since the precision of the propensity score will decrease if the included co-variate is not associated with outcomes [329], age, frailty, comorbidity and socioeconomic status were included in calculating the propensity score. According to the previous study, age, frailty, and comorbidity are strongly associated with mortality. Socioeconomic status is a proxy indicator of other confounding factors, such as body weight, smoking, etc., associated with mortality [330, 331].

Step 2: Balance the propensity score between the two treatments.

Once the propensity score has been calculated for each observation, there must be an overlap in the range of propensity scores between two treatments (called “common support”) [329]. If no patients have similar propensity scores, the inferences about treatment effects cannot be estimated [329]. In addition, the propensity score should have a similar distribution (“balance”) between the two treatments. A rough estimate of the propensity score’s distribution can be obtained by splitting the sample into quintiles of the propensity score.

Patients with two treatments (i.e., surgery and PET) were split by certain "blocks" (in general, by quintiles of the propensity score) [329]. If the propensity score of the block cannot be balanced, iterations of the distribution were conducted to balance each block [329]. The standardised mean difference (SMD) of co-variates for the treatment group and comparison group (i.e., surgery and PET) before and after weighting by propensity score was used to check whether the blocks were balanced. Generally, the difference of

SMD with less than 10% was considered co-variates well-balanced because there is no standard regarding how much imbalance is acceptable in a propensity score [332].

Step 3: Calculate the inverse probability of treatment weight (IPTW).

IPTW aims to balance the treatment and control groups by assigning weights to each participant based on their probability of receiving the treatment [328]. The process of calculating IPTW involves estimating the propensity scores, which represent the probability of receiving the treatment given the observed covariates. The inverse of the propensity score is then used as a weight for each participant. According to the IPTW estimator, the treated patients were weighted as 1/propensity score and untreated patients as 1/(1- propensity score) [333]. The idea behind this weighting is to up weight the control group participants who have a low probability of receiving the treatment and down weight the treated group who have a high probability of receiving the treatment. IPTW estimates the average treatment effect (ATE) for the entire sample [334], which provided a pseudo cohort with similar patient characteristics (i.e., make selected co-variates similar). The ATE is the estimated average effect of patients with PET on outcomes (mortality) for the patients regardless of age, frailty, comorbidity and socioeconomic status. Applying this weight when conducting regression models reduces or removes the impact of selected confounders.

In the match cohort study, Kaplan-Meier (KM) method was used to present survival between the study cohort (stratified by two initial treatments) and matched cohort (i.e., women without cancer) and tested the difference in the crude cumulative overall survival [335]. Cox's proportional hazard (PH) model assessed the ACM rate between the study cohort and matched cohort, considering treatments (surgery and PET), age strata (with

5-year intervals), three levels of CCI and HRFS, and five levels of IMD. Results were presented in hazard ratios (HR) and 95% confidence interval (95%CI).

For the cancer cohort analysis, KM survival analysis tested the difference in the cumulative overall survival OS and BCSM probabilities adjusted for covariates using the doubly robust estimation (regression adjustment and propensity score weighting) [336]. Cox's PH model was used to estimate the HR of ACM and BCSM between surgery and PET at different levels of HFRS and CCI. The proportional hazard assumption of Cox PH regression, i.e., the HR is constant with time, was examined using the Schoenfeld residuals test, which assesses the independence between residual and time and the test results are presented in p-value [337]. In the Schoenfeld residuals test, a $P<0.05$ implies that the covariates violate the proportional hazard assumption, i.e., the hazard ratio of each category within each covariate compared to the reference group changes with time [337, 338]. If the $P<0.05$ in the Schoenfeld residuals test, then a time-varying Cox PH regression was performed. All statistical analyses were performed with Stata 14.0 (Stata Corp, College Station, TX).

6.4 Results

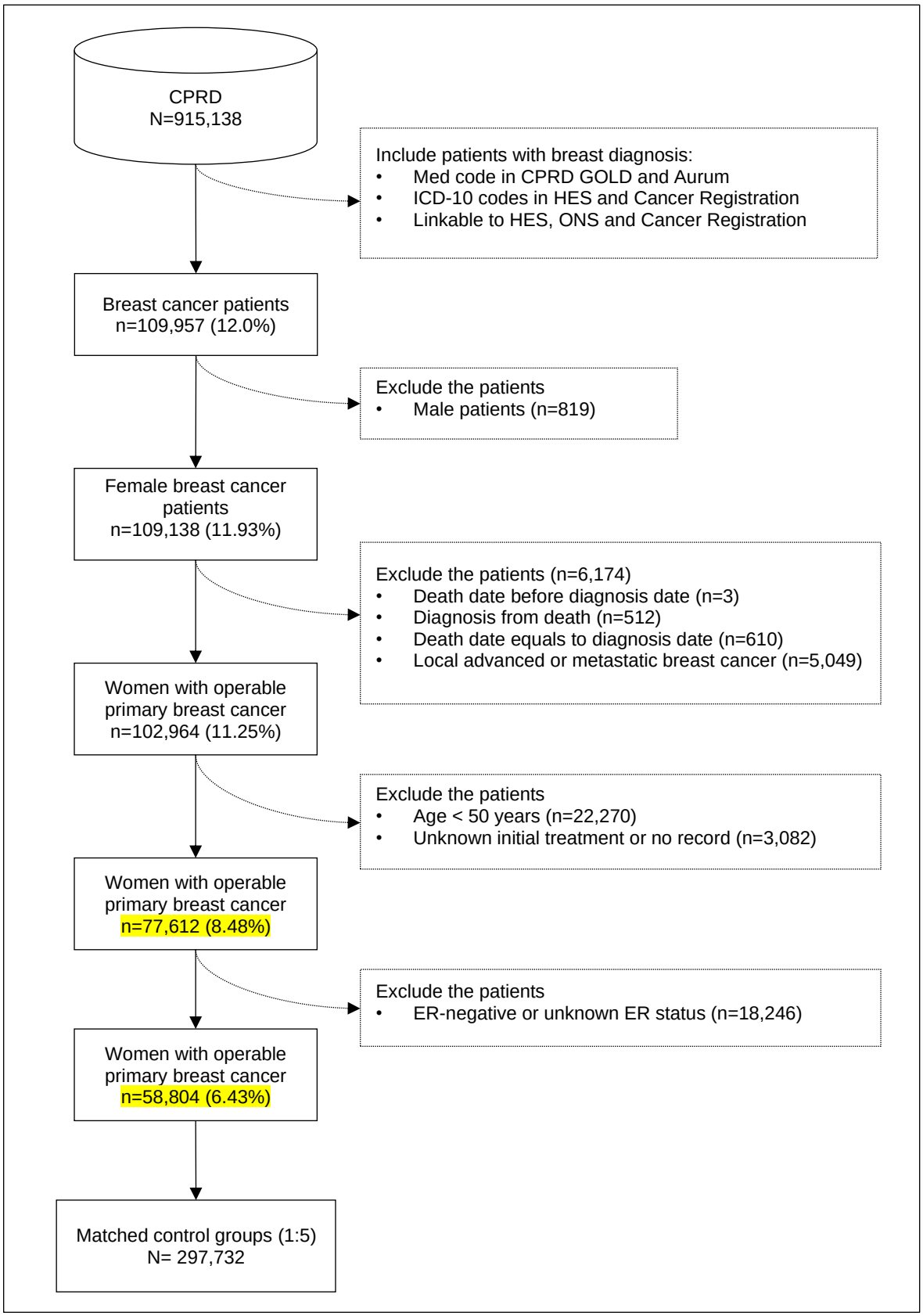
6.4.1 Characteristics of study cohort and matched cohort

Overall, 58,804 patients with early-stage breast cancer (study cohort) and 297,732 women without cancer (matched cohort) were included (Figure 6.5). According to the statistical power calculation, the large sample size in the thesis ensures good statistical power (>99%). (Detailed tumour characteristics were reported in Appendix 24)

The study cohort and their matches were well-balanced, with a p-value> 0.05 (Table 6.1). Besides, the proportion (39.3% and 37.2%) of older women was similar between the study and matched cohorts. Most of the older women with early-stage breast cancer had

a lower level of HFRS (non-frail: 93.3%, pre-frail: 12.8%), and only 3.9% were frail patients. Similarly, the majority had a lower level of CCI (low: 77.3%; intermediate: 17.8%) and only 5.0% with a high level of CCI.

Figure 6.5. Flow diagram of the study cohort and control group



(Note) CPRD: Clinical Practice Research Datalink, HES: Hospital Episodes Statistics, ONS: Office for National Statistics, ICD: International Classification of Disease, ER: Oestrogen receptor.

Of the breast cancer cohort, surgery was the primary treatment strategy (84.1%, n=49,347) compared with PET (15.9%, n=9,367), and the proportion of patients with PET rose with age increases (Figure 6.6). When stratifying by different age groups, the proportion of younger patients who received PET and surgery was 7% (n=2,354) vs 93% (n=33,341), in contrast to 30% (n=7,013) and 70% (n=16,096) in older patients, respectively. Moreover, the proportion of patients who received PET increased with age. Stratifying by 5-year interval in age, the proportions of patients receiving PET remained stable (7%) in the younger group (50-69 years) but increased from 10% at the age of 70 years to 73% at age ≥ 90 years (Figure 6.6) (Details of treatments of study cohort by age group reported in Appendix 25)

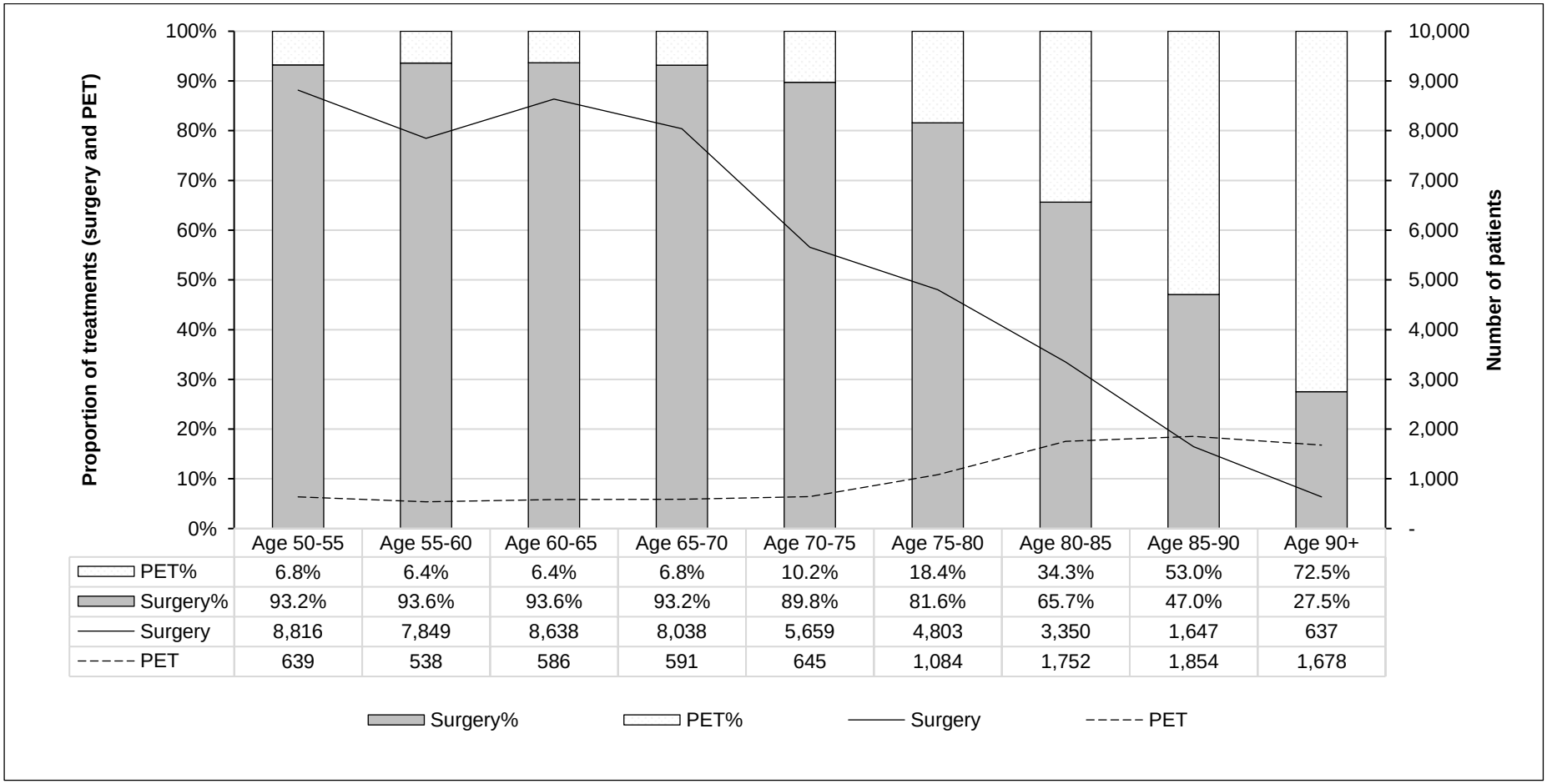
In both age strata, women without cancer had a better physical functioning profile, followed by patients with breast cancer who received surgery and PET. The median CCI and HFRS showed no significant difference in younger study and matched cohorts (p=0.68 and 0.64). On the contrary, these two measures were lower in older patients receiving surgery (2.0 [IQR: 2-3]; 2.9 [IQR: 1.5-5.4]) with a statistical difference, followed by older women without cancer (2.0 [IQR: 2-3]; 3.5 [IQR: 1.7-7.9]) and older patients with PET (3.0 [IQR: 2-4]; 5.5 [IQR: 2.3-11.2]). Besides, the IMD for younger and older study and matched cohorts were similar without a statistical difference.

Table 6.1. Characteristics of study cohort and matched cohort

Factors	Younger postmenopausal women (aged 50-69 years)					Older postmenopausal women (aged ≥70 years)				
	Matched cohort (N=186,854)	Study cohort (N=35,695)				Matched cohort (N=110,878)	Study cohort (N=23,109)			
		Surgery (n=33,341)	PET (n=2,354)	P value	SMD		Surgery (n=16,096)	PET (n=7,013)	P value	SMD
Age										
Median (IQR)	59 (54-64)	60 (54-64)	59.5 (54-65)	0.557	-	78 (74-84)	77 (73-82)	85 (80-89)	<0.001	-
Mean (SD)	59.2 (5.8)	59.3 (5.8)	59.4 (5.9)		-	79.4 (6.7)	77.8 (5.9)	84.3 (6.8)		-
CCI										
Median (IQR)	2.0 (2-2)	2 (2-2)	2 (2-2)	0.68	-	2.0 (2-3)	2 (2-3)	3 (2-4)	<0.001	-
Low (0-2)	98.5%	94.5%	93.4%	0.03	0.002	92%	80.4%	70.2%	<0.001	0.002
Intermediate (3-4)	1.3%	4.7%	5.1%	0.334	0.002	6.9%	16.0%	21.8%	<0.001	0.002
High (≥5)	0.2%	0.8%	1.4%	0.001	-0.008	1.1%	3.6%	8.0%	<0.001	-0.008
HFRS										
Median (IQR)	2.1 (1.1-3.6)	2.0 (1.1-3.2)	1.95 (1.2-3.8)	0.118	-	3.5 (1.7-7.9)	2.9 (1.5-5.4)	5.5 (2.3-11.2)	<0.001	-
Non-frail (0-5)	96.4%	97.1%	95.6%	0.064	0.011	84%	89.4%	69.6%	<0.001	0.013
Pre-frail (6-15)	3.2%	2.7%	3.5%	0.028	-0.012	11.8%	9.1%	21.2%	<0.001	-0.012
Frail (≥15)	0.4%	0.2%	0.9%	<0.001	-0.014	4.2%	1.5%	9.2%	<0.001	-0.014
IMD										
Median (IQR)	4.0 (2.0-7.0)	4 (2-7)	4 (2-6)	0.34	-	5.0 (2.0-7.0)	5 (2-7)	5 (3-8)	0.129	-
1-2	26.6%	21.9%	28.3%	0.003	0.051	23.7%	20.6%	18.7%	0.001	0.051
3-4	23.0%	18.4%	20.3%	0.02	0.014	22.3%	18.4%	17.6%	0.182	0.014
5-6	20.3%	16.2%	15.9%	0.636	-0.006	20.8%	16.0%	16.3%	0.482	-0.006
7-8	16.9%	7.5%	6.7%	0.135	-0.019	18.1%	7.8%	7.9%	0.681	-0.019
9-10	13.1%	10.1%	7.9%	<0.001	-0.042	15.0%	10.9%	14.5%	<0.001	-0.042
Missing	0.1%	25.9%	21.0%	<0.001	-0.059	0.10%	26.5%	25.0%	0.006	-0.059

(Note) PET: primary endocrine therapy; IQR: Interquartile range; SD: standard deviation; SMD: standardised mean difference; CCI: Charlson comorbidity index; HFRS: Hospital frailty risk score; IMD: Index of multiple deprivations.

Figure 6.6. Initial treatment varied by age groups



	Age 50-55	Age 55-60	Age 60-65	Age 65-70	Age 70-75	Age 75-80	Age 80-85	Age 85-90	Age 90+
PET%	6.8%	6.4%	6.4%	6.8%	10.2%	18.4%	34.3%	53.0%	72.5%
Surgery%	93.2%	93.6%	93.6%	93.2%	89.8%	81.6%	65.7%	47.0%	27.5%
Surgery	8,816	7,849	8,638	8,038	5,659	4,803	3,350	1,647	637
PET	639	538	586	591	645	1,084	1,752	1,854	1,678

(Note) PET: Primary endocrine therapy.

6.4.2 Mortality rates in older and younger postmenopausal women with breast cancer or without cancer

The ACM rate was significantly higher in the study cohort (36.4%; n=21,391) than in their matched cohort (26.6%; n=79,193); unsurprisingly, it was also higher in older than younger women. Of the matched cohort with a death record (n=79,193), 22.7% and 77.3% were younger and older; 31.3% and 68.7% were in the study cohort with a death record (n=21,391).

Furthermore, only 1% (n=8,576) was recorded as BCSM in the study cohort who died, of which 41.5% (n=3,560) and 58.5% (n=5016) BCSM cases were in younger and older patients, respectively. Therefore, older patients had higher mortality rates (ACM & BCSM) than younger patients. Also, there were no statistical differences in ACM (p=0.07) and BCSM (p=0.32) between younger and older patients with PET, respectively, and no statistical difference in BSCM of surgery between younger and older frail patients (p=0.12). (Table 6.2)

Table 6.2. Death cases and median survival time of the study cohort and control group

Factors	Younger postmenopausal women (aged 50-69 years)			Older postmenopausal women (aged ≥ 70 years)		
	Matched cohort (N=186,854)	Study cohort (N=35,695)		Matched cohort (N=110,878)	Study cohort (N=23,109)	
		Surgery (n=33,341)	PET (n=2,354)		Surgery (n=16,096)	PET (n=7,013)
Death records						
All-cause	17,976 (9.62%)	6,702 (18.78%)		61,217 (55.21%)	14,689 (63.56%)	
		5,850 (17.55%)	852 (36.19%)		8,654 (53.76%)	6,035 (86.05%)
Breast-cancer specific	-	3,560 (9.97%)		-	5,016 (21.71%)	
		2,970 (8.91%)	590 (25.06%)		2,699 (16.77%)	2,317 (33.04%)
Median survival time (IQR)						
Overall survival	9.0 (5.0-12.8)	6.6 (3.5-10.5)	2.7 (1.2-5.8)	5.7 (2.7-9.5)	5.3 (2.7-8.8)	2.3 (1.0-4.5)
Breast cancer-specific		5.3 (3.0-8.6)	2.4 (1.1-4.6)		3.7 (2.0-6.4)	1.9 (0.7-3.8)

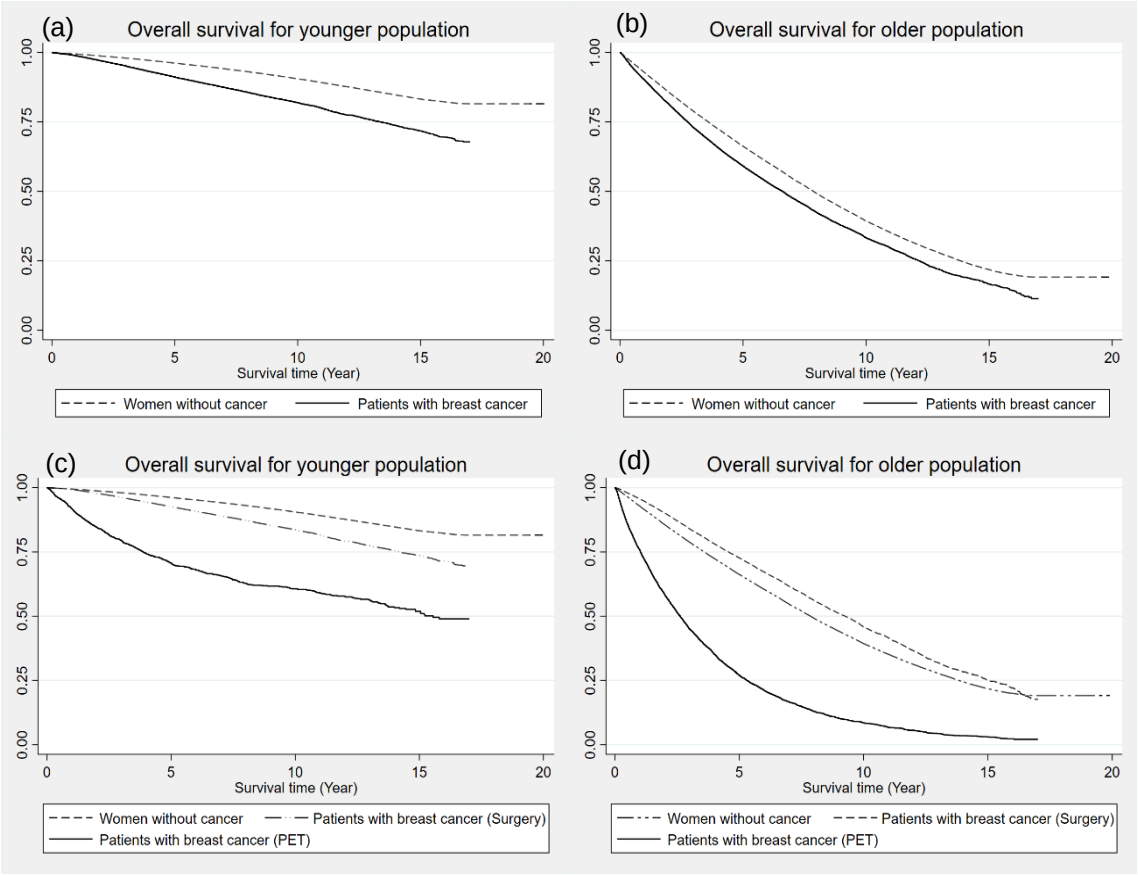
(Note) IQR: interquartile.; PET: Primary endocrine therapy

6.4.3 Overall survival time and factors associated with all-cause mortality risk in the study and matched cohorts

In line with the mortality rates, the overall survival (OS) time in the study cohort was inferior to their matched cohort, regardless of the age groups (Figure 6.7; a and b). Moreover, in the study cohort, patients who received surgery had a longer survival time than PET in both age groups (Figure 6.7; c and d). Notably, in older patients with breast cancer, the 5-, 10- and 15-year survival probabilities in patients receiving surgery (65.8%, 33.5% and 10.6%) were superior to that of the matched cohort (58.3%, 27.2% and 9.0%) and patients receiving PET (Figure 6.7; d). In this case, the different survival outcomes between PET and surgery would vary by different levels of frailty and comorbidity.

The poorer physical functioning (i.e., high-level comorbidity and frail patients) and socioeconomic status were significantly associated with the higher ACM rate (Table 6.3). In both study and matched cohorts, higher levels of CCI and HFRS were associated with a higher HR of ACM, while various IMDs were associated with a stable HR of ACM rate (range: 1.0 to 1.8 in both age groups). Moreover, the study cohort receiving PET had a significantly higher risk of ACM than those receiving surgery in both younger (HR: 2.4; 95%CI: 2.1, 2.4) and older (HR: 1.9; 95%CI: 1.8, 2.0) patient groups (Table 6.3). Except for the age, the p-value of the Schoenfeld residuals test for the covariates was >0.05, which means the hazard ratio of each category within each covariate compared to the reference group is constant with time. (Details of survival rate reported in Appendix 26, and death cases and mortality rate reported in Appendix 27)

Figure 6.7. Overall survival curves of the study and matched cohorts and stratifying frailty and comorbidity levels in the older study cohort



(Note)

PET: Primary endocrine therapy

(a) Overall survival for younger study and matched cohorts

(b) Overall survival for older study and matched cohorts

(c) Comparing the overall survival between the younger matched cohort and study cohort stratified by initial treatments received

(d) Comparing the overall survival between older matched cohort and study cohort stratified by initial treatments received

Table 6.3. Cox regression of all-cause mortality rate in the study and matched cohorts

Factors	Younger postmenopausal women (aged 50-69 years)				Older postmenopausal women (aged ≥ 70 years)			
	Matched cohort		Study cohort		Matched cohort		Study cohort	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
Age	1.1 (1.1, 1.1)	<0.001	1 (1.0, 1.1)	<0.001	1.1 (1.1, 1.1)	<0.001	1.1 (1.1, 1.1)	<0.001
Age (time-varying)	1.0 (1.0. 1.0)	0.001	1.0 (1.0. 1.0)	<0.001	1.0 (1.0. 1.0)	0.006	1.0 (1.0. 1.0)	0.108
Treatment of PET (reference: surgery)	NA	NA	2.4 (2.1, 2.4)	<0.001	NA	NA	1.9 (1.8, 2.0)	<0.001
Frailty (reference: non-frail)								
Pre-frail	2.1 (2.0, 2.3)	<0.001	1.5 (1.3, 1.8)	<0.001	1.5 (1.5, 1.6)	<0.001	1.4 (1.3, 1.5)	<0.001
Frail	5.8 (5.1, 6.5)	<0.001	3.3 (2.4, 4.6)	<0.001	2.5 (2.4, 2.6)	<0.001	2.0 (1.9, 2.2)	<0.001
CCI (reference: low level)								
Intermediate	1.7 (1.6, 1.8)	<0.001	1.6 (1.5, 1.7)	<0.001	1.2 (1.1, 1.2)	<0.001	1.3 (1.3, 1.4)	<0.001
High	2.7 (2.3, 3.1)	<0.001	2.9 (2.5, 3.2)	<0.001	1.6 (1.5, 1.7)	<0.001	1.8 (1.7, 1.9)	<0.001
IMD (reference: IMD decile 1-2)								
3-4	1.1 (1.1, 1.2)	<0.001	1.2 (1.1, 1.3)	<0.001	1.1 (1.1, 1.1)	<0.001	1.0 (1.0, 1.1)	<0.001
5-6	1.3 (1.2, 1.4)	<0.001	1.2 (1.1, 1.3)	<0.001	1.1 (1.1, 1.2)	<0.001	1.0 (1.0, 1.1)	<0.001
7-8	1.6 (1.5, 1.6)	<0.001	1.5 (1.4, 1.6)	<0.001	1.7 (1.1, 1.2)	<0.001	1.1 (1.0, 1.2)	<0.001
9-10	1.8 (1.9, 2.1)	<0.001	1.7 (1.5, 1.8)	<0.001	1.2 (1.2, 1.3)	<0.001	1.2 (1.1, 1.3)	<0.001
No observations	0.7 (0.3, 1.5)	0.302	1.5 (1.4, 1.6)	<0.001	1.6 (1.3, 2.1)	<0.001	1.2 (1.1, 1.3)	<0.001

(Note) HR: hazard ratio; CI: confidence interval; PET: primary endocrine therapy; HFRS: hospital frailty risk score; CCI: Charlson comorbidity index; IMD: index of multiple deprivations; NA: not applicable.

6.4.4 Comparative all-cause and breast cancer-specific mortality between surgery and PET in older patients with breast cancer

After the propensity score matching, 16,096 older patients receiving surgery were matched to 9,367 patients receiving PET. All the covariates (5-year intervals of age, three levels of CCI and HFRS, and five levels of IMD) were well balanced by IPTW, with the SMD less than 0.1. (Mean value and standardised mean difference of selected covariates in propensity score before and after balance reported in Appendix 28)

Older patients receiving surgery had a significantly longer median OS time (years) than their matched PET counterparts in most patients who were classified as non-frail (6.8 [IQR: 4.0, 10.6] vs 3.2 [IQR: 1.4-6.0]) and with a low level of CCI (7.0 [IQR: 4.0, 10.9] vs 3.0 [IQR: 1.2-5.6]). Likewise, surgery was associated with a longer OS time than PET for those who were frail (2.8 [IQR: 1.6-4.8] vs 1.7 [IQR: 0.7-3.0]) and at the highest level of CCI (3.8 [IQR: 2.2, 6.1] vs 2.3 [IQR: 1.0-3.8]) (Figure 6.8; a and b). Similarly, surgery had a significantly lower BCSM rate than PET counterparts (Figure 6.8; c and d).

Interestingly, despite a significant difference in OS rates for frail older patients or at the highest level of CCI, the difference in OS for surgery or PET gets closer at the 10-year OS rate (3.0% vs 1.3%) and 10-year BCSM rate (48.9% and 57.3%). Likewise, for older patients at the highest level of CCI, the 10-year OS rate (3.6% vs 2.0%) and the 10-year BCSM rate (50.9% vs 57.8%) were similar between those receiving surgery and PET.

After adjusting covariates in Cox regression, older patients receiving PET showed a significantly higher mortality risk than those receiving surgery. The comparative risk of ACM between PET and surgery declined while the levels of HFRS and CCI increased. The HRs comparing PET with surgery reduced from 3.0 (95%CI: 2.8, 3.2) in older patients at the non-frail level to 1.2 (95%CI: 0.9, 1.8) at the frail level; and from 3.0

(95%CI: 2.8, 3.3) at the low CCI level to 1.5 (95%CI: 1.1, 2.1) at the high CCI level (Table 6.4).

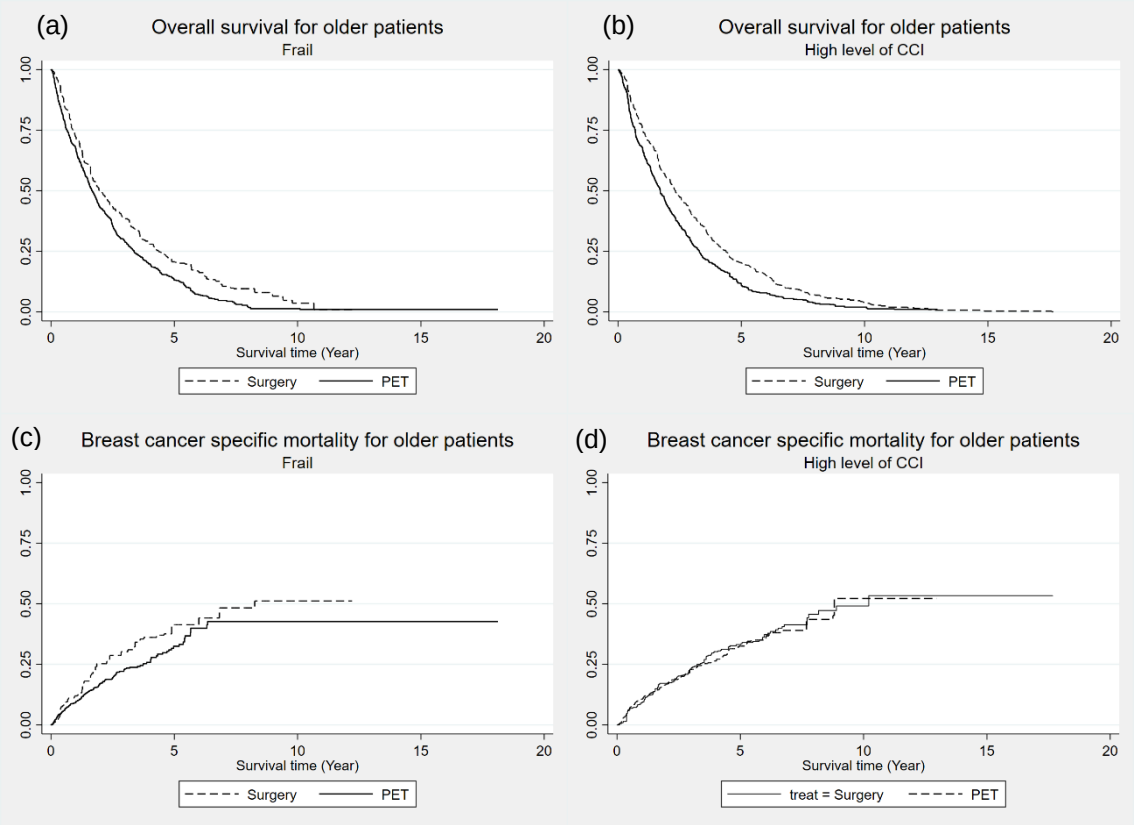
Similarly, the comparative risk of BCSM between PET and surgery was reduced while the levels of HFRS and CCI increased. Notably, there was no statistical difference in BCSM between PET and surgery for older patients at the level of frailty. The p-value of the Schoenfeld residuals test for the covariates was >0.05, which means the hazard ratio of each category within each covariate compared to the reference group is constant with time. (Table 6.4)

Table 6.4. The mortality risk of primary endocrine therapy compared with surgery by three levels of frailty and Charlson comorbidity index

Group		All-cause mortality		Breast cancer-specific mortality	
		HR (95%CI)	P-value	HR (95%CI)	P-value
HFRS	Non, frail (0, 5)	2.1 (2.0, 2.2)	<0.0001	3.0 (2.8, 3.2)	<0.0001
	Pre, frail (6, 15)	1.9 (1.7, 2.1)	<0.0001	2.1 (1.7, 2.5)	<0.0001
	Frail (≥15)	1.2 (1.1, 1.5)	0.006	1.2 (0.9, 1.9)	0.251
CCI	Low level of CCI	2.1 (2.0, 2.2)	<0.0001	3.0 (2.8, 3.2)	<0.0001
	Intermediate level of CCI	1.9 (1.7, 2.1)	<0.0001	2.2 (1.9, 2.6)	<0.0001
	High level of CCI	1.4 (1.2, 1.7)	<0.0001	1.5 (1.1, 2.1)	0.015

(Note) HR: hazard ratio; CI: confidence interval; HFRS: hospital frailty risk score; CCI: Charlson comorbidity index.

Figure 6.8. Overall survival and breast cancer-specific mortality curves between surgery and PET in older patients with high-level frailty and comorbidity



(Note)

PET: Primary endocrine therapy

(a) Overall survival for the study cohort who are frail by surgery and PET

(b) Overall survival for the study cohort who are at the high level of Charlson comorbidity index by surgery and PET

(c) Breast cancer-specific mortality for study cohort who are frail by surgery and PET

(d) Breast cancer-specific mortality for the study cohort who are at the high level of Charlson comorbidity index by surgery and PET

6.5 Discussion

The matched cohort study further elucidated that 70-year seemed to be the appropriate cut-off age defining “older women with early-stage breast cancer” since the proportion of the use of PET showed a steep increase (from 10% at 70years to 70% at 90+ years) after the age of 70 years than age below 70 years (7%). There was no statistical difference in age, frailty and comorbidity in younger postmenopausal women with early-stage breast cancer.

In line with previous observational studies [113-118], the matched cohort study found that frailty and comorbidity were associated with using PET and OS in older postmenopausal women with early-stage breast cancer. There were apparent differences in frailty, comorbidity and OS between younger and older women comparing the study cohort and their matched cohort. Notably, in older patients with breast cancer, the OS of older patients receiving surgery was superior to older women without cancer.

Consequently, a further cohort study assessed the comparative effectiveness of PET versus surgery on ACM and BCSM, targeting older patients with breast cancer stratified by different levels of frailty and comorbidity. In older patients with breast cancer, although PET was inferior to surgery considering the risk of ACM in those with lower levels of frailty and comorbidity, the hazard was reduced in those with high levels of frailty or comorbidity. Moreover, in frail older patients, there was no significant difference in the risk of BCSM between those receiving PET and surgery. Therefore, frailty and comorbidity are the critical risk factors influencing the survival of frail older patients with breast cancer. PET could be an appropriate treatment for frail patients with breast cancer or who have a heavy comorbidity burden.

For the matched cohort study, the thesis had some strengths. First, the thesis provided insight into the survival of healthy women without cancers compared to women with breast cancer. As a matched cohort study, matching minimises the confounding between a healthy population and patients with breast cancer. In this thesis, for all the women with or without breast cancer, age and general practice were matched to control the confounders from age variation and medical bias by different general practitioners to enhance the internal validity of causal inference. This finding can inform healthcare professionals to allocate the appropriate healthcare services to the older population and can be used as a basis for future healthcare studies on older populations. In addition, stratified by two initial treatment strategies for older women with breast cancer, The

matched cohort study found that surgery patients had better survival benefits than non-cancer matches and patients receiving PET. This matched cohort study elucidated that physical functioning will strongly bias the initial treatment strategy selection leading to a different survival consequence, which provided an insight into the study design in analysing cancer cohort with two initial treatment strategies.

For the analysis within the breast cancer cohort, this study strengthens the NICE clinical guideline [3] that surgery has better clinical effectiveness (overall survival) for operable patients with a good physical condition, irrespective of age. According to the results of Chapter 5, for operable patients who are physically fit for surgery, surgery is the cost-effective strategy compared with PET. Nevertheless, this study found a small proportion of patients with poor physical conditions (high levels of HFRS and CCI) receiving surgery and better physical conditions (low levels of HFRS and CCI) receiving PET. These results are probably due to the lack of comparative clinical effectiveness evidence between surgery and PET and clear consensus on managing frail patients with breast cancer [7-11]; also, surgeons' concerns about the surgical impacts on quality of life [13], and older patients' preference for minimal disruption of life [81]. A completed assessment of the clinical and cost-effectiveness of PET versus surgery in frail older patients can provide additional evidence to inform shared decision-making on geriatric breast cancer management.

Using frailty or comorbidity alone as a single index to assess the feasibility of surgery for older patients is inappropriate. Frailty and comorbidity are clinical manifestations of two distinct ageing-related processes: diminished functional reserve and accumulation of pathological processes [339]. These often co-exist in older people and impair their quality of life and functional status [339]. A cross-sectional study reported that among community-dwelling seniors who are frail, 82% have comorbidities [340]. Although co-morbidity is a key risk factor, including the pre-operative assessment in routine clinical

practice, to evaluate the feasibility of surgery that the probability will lead to postoperative complications or mortality [341], frailty assessment has been a wildly accepted indicator in routine clinical practice for old patients with cancer as a potential prognosis factor to help in choosing the appropriate treatment [74].

Therefore, a comprehensive geriatric assessment (CGA) is necessary as a pre-operative assessment for evaluating the feasibility of surgery for older patients with breast cancer. The geriatric assessment (CGA) with six domains, including physical, mental, functional, mobility, socioeconomics and medication review, is now recommended in England as an effective tool kit for pre-operative assessment [342]. In CGA, co-morbidities, frailty, and patient preference are well-integrated to represent the treatment co-preference of patients and clinicians in clinical decision-making. The CGA covers almost all the risk factors that influence the prognosis of different treatments and involves the patient preference to provide the most appropriate patient-centred treatment for geriatric patients.

This population-based study uses primary care databases linked to the hospital data, national cancer registration and death registration data in England to provide better statistical power than the previous observational study [112, 343, 344]. The cohort sample size provided good statistical power and representation of female patients with breast cancer in England through a consistent surgical treatment proportion with the national audit report of older women with breast cancer (2020) [19]. The confounding by indication in patients receiving PET and surgery was managed by the propensity score (calculated using IPTW to predict the likelihood of receiving two treatments) matching and weighting in regression adjustment. This doubly robust adjustment [336] makes the survival outcomes comparable to the identical characteristics of two age strata by minimising the confounders (age, frailty, comorbidity and socioeconomic status) between exposure and outcome.

However, there are some limitations to this study. First, matching, as an approach, will lose a group of sampling that may not be matched, leading to biased results. In addition, matching will limit the number of confounders included in the matching process. This thesis only selected three variables to match, and this may not perfectly reflect the influence on the survival consequences. There is some unmeasured confounding (e.g., diet habits, smoking and alcohol status, obesity, psychological status) that can impact the survival benefits for both the cancer cohort and non-cancer cohort [32]. Nonetheless, regression was used in this matched cohort study to adjust covariate variables (e.g., comorbidity and frailty) that can reflect the impact of such unmeasured confounding as smoking, alcohol status, and obesity on physical conditions. Therefore, the results of the matched cohort study showed the value of the current healthcare system. In addition, matched cohort study revealed the association between women with or without breast cancer and survival consequences, but the influence of breast cancer on survival may not be quantified due to insufficient information.

For the breast cancer cohort analysis, there are also some limitations. First, this study did not include the patient-reported outcome measures (such as the health-related quality of life and postoperative functional status) and other cancer-specific outcomes (such as disease-free and progression-free survival). This is because these data were not routinely collected in the study databases. Hospital medical records may be a valuable source for identifying the progressed event of cancer progression or metastasis.

Second, although frailty and comorbidity commonly represent physical functioning in clinical practice, physical functioning as a complicated physical status may not entirely and accurately be quantified using only two indicators. Frailty and comorbidity in the thesis only represented a crucial aspect of patient physical functioning. Physical functioning also includes the body's movement ability and quality of life [345]. In addition,

although frailty or comorbidity was estimated in the thesis using the published validated algorithm [76, 325], the frailty and comorbidity status for the patients in the real world may not be accurately quantified through the limited data source. Therefore, the thesis only analysed the results based on the patients with represented frailty or comorbidity status to inform the decision-making of treatments in older patients.

The final limitation of this chapter is how the confounding was controlled, which is an inherent limitation in observational studies. The first challenge in the thesis for confounding control is balancing the selection and misclassification bias in the analysis. This thesis selected PET and surgery as the initial treatment strategies, irrespective of what the subsequent treatment received. However, the reality may be that for some older patients initially receiving PET; then surgery would be given if the breast cancer progressed. Specific to this group of patients who received PET within one year but received surgery after one year, they were excluded from the study cohort to minimise the misclassification bias.

Meanwhile, this thesis focused on older patients who are unfit for surgery. According to expert opinions, frail patients treated by PET due to unfit for surgery after diagnosis are unlikely to be treated by surgery. Thus, misclassification bias may not influence the study cohort identification. Also, by the propensity score weighting, selection bias can be recognised as well-controlled in the thesis.

The second challenge of the confounding is the immortal bias. The immortal bias may not be vastly influential on the results. Immortal bias is "*the error in estimating the association between the exposure and the outcome that results from misclassification or exclusion of time intervals*." [346]. Specific to the thesis, the immortal bias is that there were potential outcome measures (i.e., death) before treatment started. In this thesis, only patients with PET may introduce immortal bias because surgery is the event

observed as exposure and patients were excluded if are dead before surgery. For the patients classified as PET, there was little likelihood that patients who used ET as neo-adjuvant treatment died before surgery onset. Therefore, immortal bias has a minor influence on the thesis.

The third challenge of the confounding is the other unmeasured confounders, such as body weight, alcohol, and smoking status. Studies indicated that the exemplified unmeasured confounders (for example, body weight, alcohol, and smoking statuses) are highly associated with socioeconomic status [347-349]. The thesis included IMD representing socioeconomic status in estimating the propensity score to minimise the influence. Also, other unmeasured confounders may impact the treatment selection according to the previously published studies and matched cohort study in the thesis but may not be influential on the thesis.

Another limitation of this chapter was that frailty and comorbidity severity vary with time. In older patients, physical functioning caused by frailty and comorbidity may worsen with time. The time-varied frailty and comorbidity were less influential to the outcomes in this study because the frailty and comorbidity identified in this chapter were the baseline states instead of identifying them by specific time intervals. This less influence can be further explained by the fact that except for age, the assumption of Cox PH regression was validated through the Schoenfeld residuals test.

A competing risk regression analysis was further conducted as a sensitivity analysis to evaluate the clinical and comparative effectiveness of PET versus surgery are consistent with that assessed by Cox PH regression. This sensitivity analysis showed similar results: no statistical difference in overall survival between surgery and PET in older patients with a high level of HFRS. The sub-distribution hazard ratio (SHR) of all-cause death events competed by non-all-cause death events was 1.2 (95% CI: 1.0-1.4, p-value: 0.082). Also,

there is no difference in the comparative effectiveness of PET compared to surgery in older patients with a high level of HFRS and CCI. The SHR of other cause death event (which is defined as any other death events identified by the non-breast cancer-specific death) competed to breast cancer-specific death events was 1.1 (95% CI: 0.9-1.4, p-value: 0.261) for patients with a high level of HFRS, and 1.1 (95% CI: 0.9-1.4, p-value: 0.093) for the patients with a high level of CCI. (Details of competing risk regression in Appendix 29)

In the future, it is necessary to comprehensively evaluate the clinical effects, such as progression-free survival and quality of life, to understand better the treatment effects of PET in older women with early-stage breast cancer. Further observational studies are valuable to identify the progression-free survival of PET using primary data sources. Besides, the cost-effectiveness analysis of surgery versus PET in frail older patients with breast cancer is needed to be evaluated to provide more potent evidence for improving the management of breast cancer in the geriatric population.

6.6 Conclusion

Consistent with clinical guideline recommendations, surgery is the optimal treatment for patients with breast cancer whose physical conditions are appropriate for surgery, irrespective of diagnostic age. However, for patients who are unfit for surgery due to frailty or multi-morbidity, irrespective of age, PET is an appropriate initial treatment due to the limited survival benefits of surgery. Furthermore, the cost-effectiveness of PET versus surgery in older patients who are physically unfit for surgery should be conducted to provide further evidence to improve the better healthcare for breast cancer management (Chapter 7).

Chapter 7 Cost-effectiveness analyses of primary endocrine therapy in older women with early-stage breast cancer and various levels of frailty

Chapter 7 reports the cost-effectiveness analysis of PET versus surgery in older patients with ER+ early-stage breast cancer who are pre-frail and frail. The chapter is presented as a standalone study in terms of an introduction (Section 7.1), aim and objectives (Section 7.2), methods (Section 7.3), results (Section 7.4), discussion (Section 7.5), and conclusion (Section 7.6).

7.1 Introduction

Although PET is commonly used for treating patients with ER+ breast cancer who are older and frailer, suggested by clinical recommendations by SIOG and EUSOMA (Chapter 6) [311], evidence-based clinical effectiveness data (i.e., RCTs) is lacking in generating economic evidence. In line with NICE guidance, leveraging evidence from observational studies that applied real-world, quality data sources to maximise sample size and a well-designed methodology to diminish the potential bias and confounders is a feasible approach to provide clinical and economic evidence for the target cohort of older breast cancer patients [350]. In the thesis, Chapter 6 conducted a cohort study that took account of selection bias to evaluate the clinical and comparative effectiveness of PET versus surgery, which can be used as the evidence data source to estimate input parameters for the model-based economic evaluation of PET versus surgery for older patients who are unfit for surgery (Chapter 7).

In addition, according to Chapter 3, there was only one published economic evaluation by Holmes *et al.* (2021) that evaluated the cost-effectiveness of PET versus surgery by age subgroups (70-, 80-, and 90-year), comorbidity levels and lymph nodal status. This economic evaluation used observational data sources [290, 351] to identify the overall survival of PET and surgery in England. The cohort study used North England's local, regional cancer registry data to estimate the overall survival. The results showed that

PET was a cost-effective strategy for older patients aged >90, irrespective of comorbidity and nodal status [180]. However, as indicated in the previous cohort study (Chapter 6), comorbidity and frailty are two critical indicators of PET in older patients. The economic evaluations, including comorbidity, may not comprehensively estimate the cost-effectiveness of PET versus surgery for older patients unfit for surgery. Thus, frailty may also be a valuable indicator to predict the cost-effectiveness of PET versus surgery in older patients who are unfit.

In Chapter 6, the clinical effectiveness of PET versus surgery by levels of frailty was categorised into three levels using ranges of HFRS: non-frail (<5), pre-frail (5-14), and frail (≥15). There was a systematic review to investigate the prevalence and its association with clinical outcomes in general surgery [352]. Of the systematic review [352], patients with frailty were pre-specified as non-frail, pre-frail and frail based on the outcomes of incidence of post-surgical complications, re-admission rate and mortality, which is identical to outcomes for HFRS (used in Chapter 6). The results of the systematic review showed that pre-frail (9%) and frail patients (24%) had a higher incidence rate of post-surgical complications than non-frail patients (4%) [352]. Also, frail patients had higher short-term (30 days) mortality (9%) compared to non-frail patients (3%), in which the data for pre-frail patients were not pooled [352]. In summary, the thesis assumed that pre-frail and frail patients are probably unfit for surgery, which was the target population in Chapter 7.

7.2 Aim and objectives

This chapter aimed to generate economic evidence of PET versus surgery for older women with ER+ early-stage breast cancer at different frailty levels. The objective included:

(1) To evaluate the cost-effectiveness of PET versus surgery in older patients stratified by the level of frailty (i.e., pre-frail and frail) using observational data sources;

(2) To estimate the value of further research to reduce decision uncertainty in these two frail populations.

7.3 Methods

7.3.1 Study design

This decision-analytic model-based CEA estimated the lifetime cost and health outcomes between PET and surgery as the initial treatment strategy in the target population of older women aged ≥70 years with HR+ early-stage breast cancer whose physical conditions are at pre-frail or frail stages. Surgery was defined as mastectomy or breast-conserving surgery with post-adjuvant ET. PET was defined as the lifetime treatment of any endocrine medications (i.e., tamoxifen 20mg daily, letrozole 2.5 mg daily, anastrozole 1mg daily or exemestane 25mg daily) excluding surgery.

The target population of this chapter was the patients who were unfit for surgery (i.e., pre-frail and frail). The criteria to define frail and per-frail were in line with the cohort study (Chapter 6), pre-frail (HFRS 5-14), and frail (HFRS ≥15). According to the NICE guidance [125], the perspective of the analysis was the National Health Service (NHS) England and Personal Social Services. Health outcomes were measured as quality-adjusted life years (QALYs). Costs and QALYs were discounted at 3.5% per year. The analysis was conducted according to the NICE reference case (Table 7.1) [83] and reported following the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [189] (Appendix 30).

Table 7.1. Decision problem for cost-effectiveness analysis

Elements of the decision problem	Description
Population	Pre-frail or frail older women (≥ 70 years) with early-stage breast cancer
Intervention	Primary endocrine therapy
Comparator	Surgery
Perspective	NHS England & Personal Social Services perspective
Measures of health outcome	EQ-5D quality-adjusted life years
Cost consideration	Include direct medical costs: • treatment cost • cost of hospitalisation Exclude direct non-medical, indirect and productivity cost
Outcome	• Expected incremental cost • Expected incremental QALYs • Incremental cost-effectiveness ratio • The expected value of perfect information
Time horizon	The lifetime with a 6-month cycle length
Discount rate	Cost=3.5%, QALYs=3.5% per year
Cost-effectiveness threshold	£20,000 to £30,000 per QALY gained
Sensitivity analysis	• one-way sensitivity analysis • probabilistic sensitivity analysis

(Note) NHS: National Health Service; QALYs: quality-adjusted life years.

7.3.2 Model structure

A Markov model simulated a hypothetical cohort of older patients (n=10,000) over their lifetimes between three mutually exclusive health states, i.e., stable (receiving treatment without local or distant progression), progressed (recurrence in the ipsilateral chest wall following mastectomy; local disease progression following PET), and dead (Figure 5.1). The model structure was identical to the one in Chapter 5. The input data for this Markov model consisted of clinical effectiveness (transition probabilities between health states), the health state utility, resource use and unit cost (Table 7.2).

7.3.3 Clinical effectiveness

The transition probabilities from the stable to the dead (P2 in Figure 5.1) by pre-frail and frail patients were estimated from the survival curves established in a cohort study (Chapter 6). The method used to estimate the most appropriate survival functions that fit the survival curves was identical to the methods depicted in Chapter 5. Five parametric survival models (Exponential, Weibull, Gompertz, Log-logistic, and Log-normal) fit the overall survival data. The most appropriate parametric survival curve was selected by reference to goodness-of-fit statistics (the lowest Akaike Information Criteria (AIC) and the Bayesian Information Criteria (BIC) values [295, 296]) and visual inspection to assess the clinical plausibility of the extrapolation [294, 297]. Weibull distributions fitted the overall survivals best for pre-frail and frail patients who received surgery or PET [16].

Transition probabilities from stable to progressed (P1 in Figure 5.1) were estimated from the survival curves established in an RCT by Chakrabarti *et al.* (2011) [99]. The RCT recruited 131 older women (aged ≥ 70 years) with early-stage breast cancer, regardless of the ER status, from the Nottingham Breast Unit in England between 1982 and 1987. Participants were randomly assigned to wedge mastectomy alone (surgery arm, n=66) and or tamoxifen alone (PET arm, n=65) and followed up for 20 years [99]. Transition probabilities from stable to progressed (P1) were assumed identical between pre-frail and frail patients because the frailty may not impact the natural history of breast cancer, progression or metastasis.

The time to progression curves in Chakrabarti *et al.*'s RCT was rebuilt using DigitizeIt® [298, 299, 356] to estimate the probability from stable to progress. The most appropriate parametric survival model with the same procedure as P2 was selected. Gompertz distributions fit the surgery arm's overall survival and progression-free survival data. For the PET arm, log-logistic and log-normal distributions best fit the overall and progression-

free survival data (Table 7.2). The transition probability over time was calculated from the hazard function [H(t)] or survival functions [S(t)] following the formula that was estimated according to the parametric survival functions [294].

The transition probability of death (P3 in Figure 5.1) from the progressed state depended on whether a patient had metastatic disease (identical to Chapter 5). The transition probability from the progressed or metastasis to the dead state was directly elicited from a previously published cost-effectiveness analysis of extended adjuvant endocrine therapy in treating postmenopausal women with HR+ breast cancer [298]. The proportion of patients who had metastasis in the progression state was directly extracted from the RCT by Chakrabarti *et al.* (2011) (42% for the surgery arm and 35% for the PET arm) [99].

7.3.4 Utility

Health utility values were measured by the EQ-5D-3L instrument [299], a preference-based instrument, valuing health from 0 (dead) to 1 (perfect state), and states worse than death are possible [135]. The utility values for the stable state were extracted from previously published literature (identical to Chapter 5) and adjusted for two levels of frailty using the multiplicative method (Chapter 3).

The original utility value for the stable state was identified from an RCT of older patients aged ≥70 years with early-stage breast cancer with or without post-surgical radiotherapy (n=85; mean age: 72.3 years, standard deviation: 5.0) conducted in the UK in 2007 [272]. The mean EQ-5D-3L utility value after receiving surgery with radiotherapy was 0.78 (95%CI: 0.72, 0.81) [272].

The stable utility multiplier for pre-frail and frail patients was calculated from a cohort study [353], which measured the utility of patients diagnosed with cardiovascular disease

at three levels of the HFRS (non-frail, pre-frail and frail) using SF-6D [353]. The ratio of SD-6D score between the frail (0.65), pre-frail (0.79) and non-frail (0.86) were assumed to be constant (pre-frail: 0.79/0.86=0.9186; frail: 0.65/0.86=0.7558) and used as the multiplier to estimate the utility values of pre-frail and frail patients in this study, although the valuation method and targeted population were different from this cost-effectiveness analysis.

Utility values for the progressed and metastasis states were estimated by additive decrements method [15, 354] based on a systematic review and meta-regression of utility values for breast cancer (disutility values for progressed disease [-0.126] and metastatic disease [-0.352]) (Table 2) [239]. To reflect the natural decline of quality of life as age increases, the decrements of age-associated health utility values were -0.0013 each year based on a meta-regression of EQ-5D utility values in older women with early-stage breast cancer (Chapter 4).

7.3.5 Resource use and cost

The cost estimates were identical to the estimates described in Chapter 5. Healthcare resource use related to different health states in the model was estimated based on the national clinical guideline for early and locally advanced breast cancer in the UK [3] (Table 5.2). The unit cost of surgery was obtained from the England NHS reference costs (2019/2020) [301], while the cost of PET was estimated based on the assumption that patients receive tamoxifen in the first five years after breast cancer is diagnosed and then may change to an aromatase inhibitor (for example, letrozole, anastrozole, and exemestane) for a lifelong treatment [3]. According to the NICE guideline, Tamoxifen was assumed to be used for the post-surgical adjuvant ET for five years. The unit cost of these medicines was obtained from the British National Formulary (BNF, November

2021, Drug Tariff) [300]. Historic prices were inflated to 2020/21 using the inflation indices published by the Personal Social Services Research Unit [303]. (Table 7.2)

7.4 Data analysis

A deterministic base-case analysis was conducted to calculate the incremental cost, life-years (LY) gained, QALYs gained, and the incremental cost-effectiveness ratio (ICER) that is calculated using incremental cost divided by incremental QALYs (Section 2.2.4, page 67). The net monetary benefit (NMB) and incremental NMB were calculated assuming a cost-effective threshold of £20,000 per QALY gained [304, 305]. Furthermore, a one-way sensitivity analysis was performed to investigate how uncertainty in the input parameter values affected the Incremental NMB (INMB) and presented in a tornado diagram. In the sensitivity analysis, transition probabilities and utility values were varied to the upper and lower values of their 95% confidence intervals. Unit costs varied by ±25% from their base case value (Table 7.2). A half-cycle correction was conducted in base case analysis to check the Markov model assumption that each cycle in the analysis is an equal discrete length of time.

A probabilistic sensitivity analysis (PSA) propagated uncertainty through all input parameters simultaneously via Monte Carlo simulation (n=10,000 iterations) [307]. Appropriate probability distributions were assigned to each input parameter (Table 7.2). The results were presented graphically using a cost-effective (CE) plane and cost-effective acceptability curve (CEAC) [160]. The expected value of perfect information (EVPI) was calculated from the probabilistic output to quantify the need for further research [308].

The estimated EVPI presented over a range of cost-effective threshold values (£0 to £30,000 per QALY gained), which represented the upper bound on the cost of further research to be cost-effective. Per-patient estimates were scaled to population-level

estimates based on the number of incident patients who could benefit from this further research. The size of the beneficiary population (population EVPI) was estimated by (1) the annual incidence of the target population; (2) the anticipated life cycle of patients who would be beneficial, which was uncertain and assumed to be up to ten years; (3) discount rate of 3.5 % based on the NICE guidance [83].

The annual incidence of older women diagnosed with early-stage breast cancer in England (n=13,396) was based on the national audit of breast cancer in older women in England (2022) [11]. The proportion of pre-frail (12.8%) and frail patients (3.9%) were estimated from the previous cohort study reported in Chapter 6. The size of the beneficiary population was estimated to be 37,460 pre-frail women and 10,334 frail women over ten years. The EVPI calculation was identical to the procedures reported in Chapter 5.

Table 7.2. Input parameters

Parameters	Deterministic analysis		Probabilistic analysis		Data source
	Value	**Range (95% CI)**	**Distribution**	**Parameters**	
Transition probabilities					
Surgery					
From disease free to death for pre-frail patients	Weibull Shape: -1.42 Scale: 1.10	shape (-1.60, -1.24) scale (1.04, 1.16)	Multivariate normal	shape: 0.0916 scale: -0.0121 cov: 0.0237	Chapter 6
From disease free to death for frail patients	Weibull Shape: 0.29 Scale: 1.06	shape (0.23, 0.37) scale (0.95, 1.17)	Multivariate normal	shape: 0.1257 scale: -0.0362 cov: 0.03826	Chapter 6
From disease free to progressed disease	Gompertz Shape: -2.59 Scale: -0.14	shape (-3.04, -2.13) scale (-0.22, -0.05)	Multivariate normal	shape: 0.2308 scale: -0.03388 cov: 0.02715	[99]
PET					
From disease free to death for pre-frail patients	Weibull Shape: -0.79 Scale: 0.95	shape (-0.96, -0.61) scale (0.90, 1.01)	Multivariate normal	shape: 0.08816 scale: -0.00795 cov: 0.02911	Chapter 6
From disease free to death for frail patients	Weibull Shape: 0.38 Scale: 1.02	shape (0.33, 0.44) scale (0.94, 1.10)	Multivariate normal	shape: 0.07395 scale: -0.02259 cov: 0.0331	Chapter 6
From disease free to progressed disease	Log-normal shape: 0.98 location: 1.39	shape (0.79, 1.22) location (1.21, 1.61)	Multivariate normal	shape: 0.1251 location: 0.007 cov:0.07135	[99]
From progressed to death	0.04	(0.035, 0.045)	Beta (α, β)	280, 6610	[298]
From metastasis to death	0.10	(0.085,0.120)	Beta (α, β)	739.5, 6150	[298]
Utility					
Stable state					
Initial utility values of stable	0.75	0.72, 0.79	Beta (α, β)	191, 63	[272]

Parameters	Deterministic analysis		Probabilistic analysis		Data source
	Value	Range (95% CI)	Distribution	Parameters	
Non-frail	0.86	0.84, 0.88	Beta (α, β)	270, 0.01	[353]
Pre-frail	0.79	0.77, 0.81	Beta (α, β)	151, 0.01	[353]
Frail	0.65	0.63, 0.67	Beta (α, β)	400, 0.01	[353]
Surgery					
Values of stable state	0.71	0.67, 0.73	Beta (α, β)	188.7, 66.3	[272], [353]
PET					
Value of stable state	0.71	0.68, 0.74	Beta (α, β)	191.25, 63.75	[272], [353]
Progressed state of surgery and PET					
Decrement value	-0.143	-0.174, -0.112	Normal (Mean, SE)	-0.143, 0.016	[239]
Metastatic state of surgery and PET					
Decrement value	-0.338	-0.373, -0.303	Normal (Mean, SE)	-0.338, 0.000685	[239]
Age decrement in 1 year	-0.0013	-0.004, 0.002	Normal (Mean, SE)	-0.0013, 0.001	Chapter 4
Cost					
Surgery	£8674.19				
Mastectomy (%)	£6547.64	Fixed value			[301], [303]
Proportion of mastectomy	35%	28%-43%	Beta (α, β)	16340, 30345	[303]
Delayed breast reconstruction of mastectomy	£12722.17	Fixed value			[301], [303]
The proportion of delayed breast reconstruction of mastectomy	85%	80%-90%	Beta (α, β)	13889, 2451	[303]
Breast-conserving surgery (%)	£3996.41	Fixed value			[301], [303]
The proportion of breast-conserving surgery	65%	1- Proportion of mastectomy			[303]
Cost of hospital stays per cycle	£937.00	Fixed value			[303], [301]
Tamoxifen (per tablet)	£0.31	Fixed value			[300], [303]
Letrozole (per tablet)	£3.12	Fixed value			[300], [303]
Cost of follow-up per cycle	£64.43	Fixed value			[301], [303]
Cost of progressed disease	£8251.75	(£5691.10-£11248.21)	Gamma (α, β)	33.88, 487.09	[302], [303]

Parameters	Deterministic analysis		Probabilistic analysis		Data source
	Value	Range (95% CI)	Distribution	Parameters	
Cost of metastatic state	£6223.54	(£4990.12-£7638.91)	Gamma (α, β)	84.83, 146.73	[302], [303]

(Note) 95% CI: 95% confidence interval; PET: primary endocrine therapy; SE: standard error

7.5 Results

7.5.1 Deterministic base-case analysis

The total lifetime cost of surgery and PET were £29,641.84 and £48,213.84 for pre-frail patients; £17,196.20 and £24,547.68 for frail patients, respectively. Consequently, the incremental costs of PET compared with surgery were £18,572 for pre-frail patients and £7,351.48 for frail patients. Regarding the outcome, the total lifetime QALYs from surgery and PET were 1.96 and 1.85 for pre-frail patients and 0.40 and 0.97 for frail patients, respectively.

Therefore, the incremental QALYs comparing PET with surgery were minus 0.11 for pre-frail patients and 0.38 for frail patients. Overall, surgery is the dominant strategy for pre-frail patients, whereas PET is a cost-effective strategy for frail patients with an ICER of £19,498.08 per QALY gained. The INMB of PET versus surgery was minus £20,734.98 for pre-frail patients and £189.24 for frail patients at a cost-effective threshold of £20,000 (Table 7.3). According to the half-cycle correction, the result was not changed: surgery is the dominant strategy for pre-frail patients, while PET is a cost-effective strategy for frail patients (Table 7.4).

Table 7.3. Base-case deterministic analysis results

Results		Surgery	PET
Pre-frail			
The expected cost of surgery (£)		£29,641.84	£48,213.84
Life year gained		4.00	4.26
Expected QALYs		1.96	1.85
Incremental cost			£18,572.00
Incremental QALYs			-0.11
ICER		Dominant	
Net monetary benefit (£)	λ=20000	£9,575.71	-£11,159.26
	λ=30000	£29,184.49	£7,368.03
Incremental net monetary benefit (£)	λ=20000		-£20,734.98
	λ=30000		-£21,816.47
Frail			
The expected cost of surgery (£)		£17,196.20	£24,547.68
Life year gained		0.96	1.90
Expected QALYs		0.35	0.72
Incremental cost			£7,351.48
Incremental QALYs			0.38
ICER			£19,498.08 per QALY gain
Net monetary benefit (£)	λ=20000	-£10,288.18	-£10,098.94
	λ=30000	-£6,834.17	-£2,874.57
Incremental net monetary benefit (£)	λ=20000		£189.24
	λ=30000		£3,959.60

(Note) QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; λ: cost-effectiveness threshold.

Table 7.4. Half cycle correction

Results		Surgery	PET
Pre-frail			
The expected cost of surgery (£)		£29,472.70	£47,748.61
Life year gained		3.78	4.06
Expected QALYs		1.82	1.72
Incremental cost			-£22,912.36
Incremental QALYs			-0.10
ICER		Dominant	
Net monetary benefit (£)	λ =20000	£6,960.03	£13,253.80
	λ =30000	£25,176.40	£3,993.61
Incremental net monetary benefit (£)	λ =20000		-£20,213.83
	λ =30000		-£21,182.79
Frail			
The expected cost of surgery (£)		£17,042.89	£24,095.67
Life year gained		0.83	1.78
Expected QALYs		0.28	0.66
Incremental cost			£11,705.07
Incremental QALYs			0.38
ICER			£18,660.50 per QALY gain
Net monetary benefit (£)	λ =20000	-£11,442.07	-£10,935.80
	λ =30000	-£8,641.66	-£4,355.87
Incremental net monetary benefit (£)	λ =20000		£506.27
	λ =30000		£4,285.79

(Note) QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; λ: cost-effectiveness threshold.

7.5.2 Sensitivity analyses

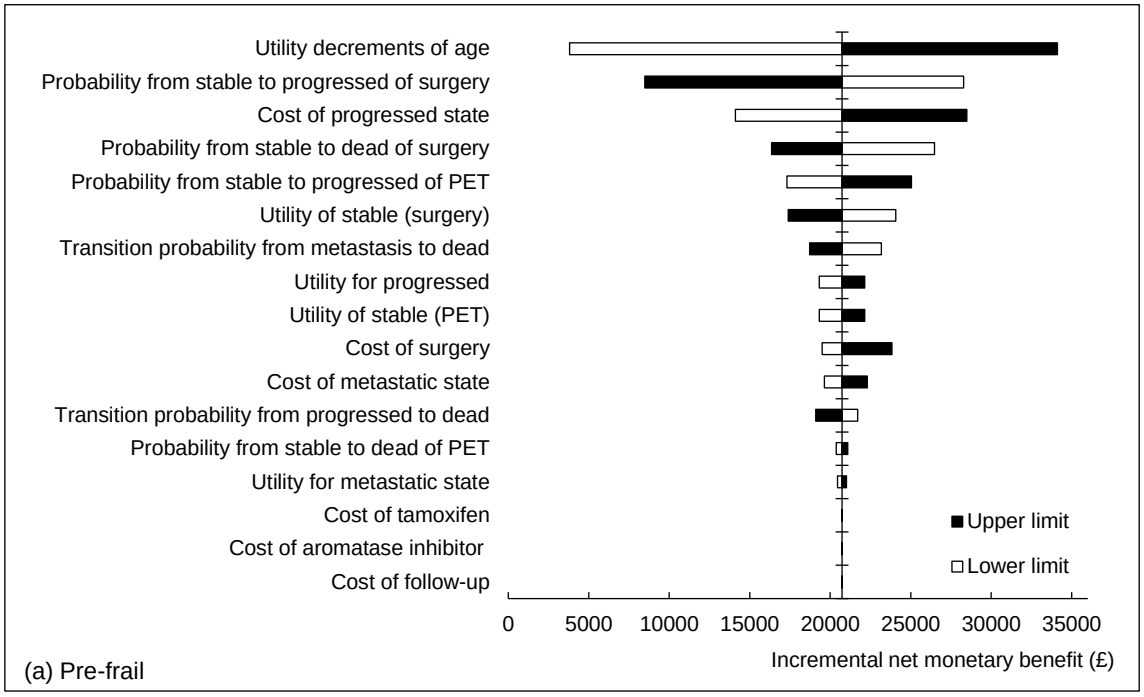
The Tornado diagram of one-way sensitivity analyses demonstrated how sensitive the INMB of surgery vs PET responds to changes in the input parameter values (Figure 7.1, a). The incremental NMB is most sensitive to the parameter uncertainty associated with the utility decrements of increasing age and the transition probabilities from the stable to progressed states for surgery. All the estimated INMB values in these sensitivity

analyses were positive for the pre-frail patients. The results of the one-way sensitivity analysis indicated that although some factors may drive the relative cost-effectiveness of surgery versus PET, the current results that surgery is a cost-effective strategy for pre-frail patients may not be changed.

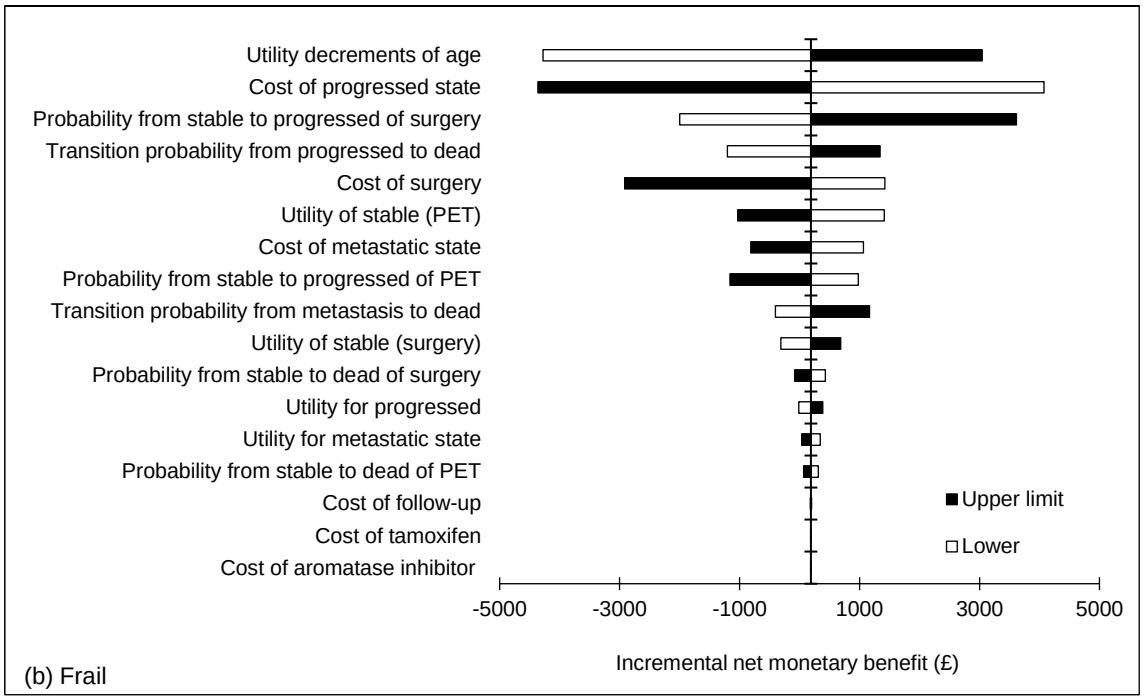
The positive NMB values imply that an intervention should be accepted as its value is more than the additional cost of the benefit. In contrast, the negative NMB values suggest that the intervention should not be accepted. However, for frail patients, the value was £189.24 for PET, which indicates that PET should be accepted at the CE threshold of £20,000. When changing the input parameters values, except for five input parameters (i.e., cost of aromatase inhibitor and tamoxifen; cost of follow-up; probability from stable to dead of PET; utility for the metastatic state), the INMB for the rest of the parameters were shifted to the negative values at the CE threshold of £20,000 (Figure 7.1, b,). These shifts demonstrated great uncertainty regarding the conclusion that PET is a cost-effective strategy for frail older patients.

According to the PSA, for pre-frail patients, almost all dots are located at the NW quadrant, which indicates that surgery is the dominant strategy compared with PET. For frail patients, since most PSA dots are distributed across the CE threshold of £20,000, it is difficult to decide which is a cost-effective strategy (Figure 7.2). According to the CEAC, at a cost-effectiveness threshold of £20,000 per QALY gained, the probability that PET is cost-effective was 64.7% for frail patients, and the probability that PET is cost-effective was 88.2% when the cost-effectiveness threshold rises at £30,000 per QALY (Figure 7.3). Therefore, PET is a relatively cost-effective strategy by PSA under certain distributions for each input parameter for frail patients.

Figure 7.1. Tornado diagram of deterministic sensitivity analysis



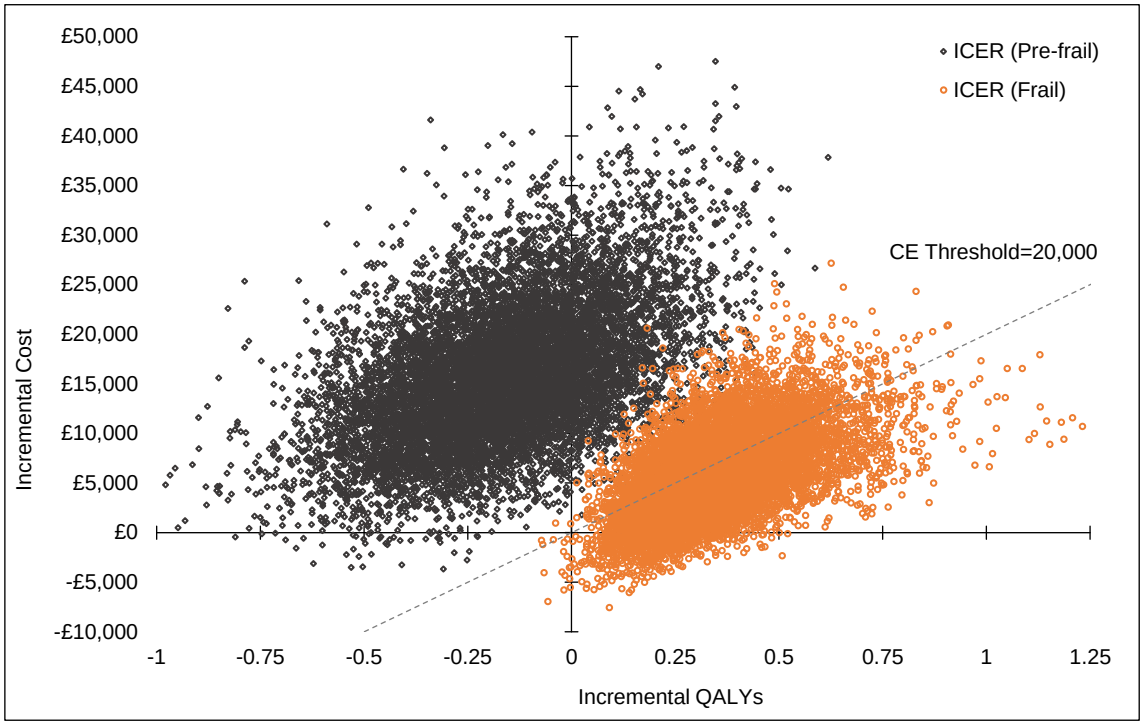
(a) Pre-frail



(b) Frail

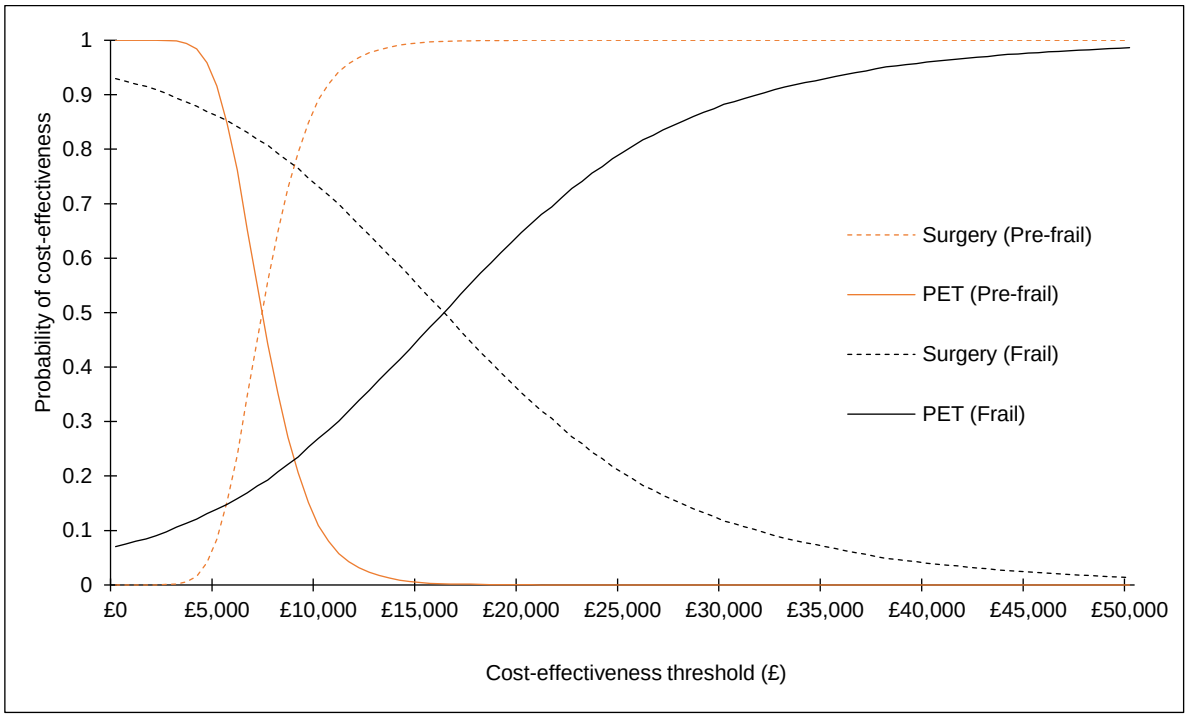
(Note) PET: primary endocrine therapy

Figure 7.2. Cost-effectiveness plane for pre-frail and frail patients



(Note) PET against surgery; ICER: incremental cost-effectiveness ratio; CE: cost-effectiveness.

Figure 7.3. Cost-effectiveness acceptability curve for pre-frail and frail patients

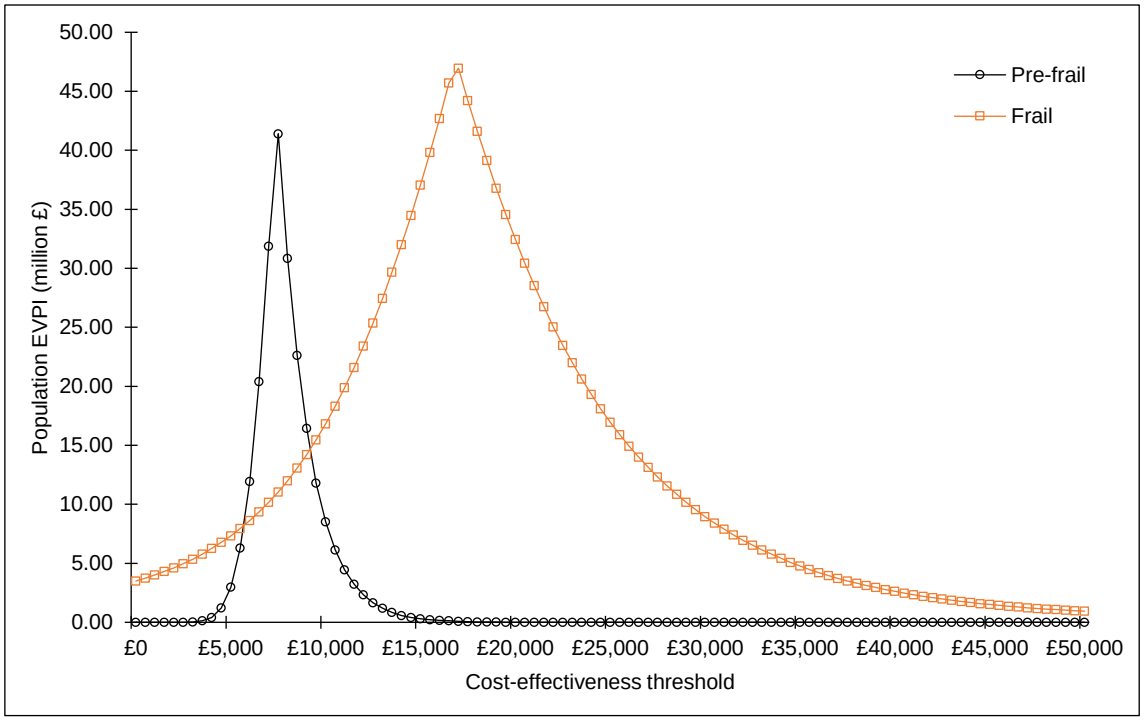


(Note): PET: primary endocrine therapy; QALY: quality-adjust life year

7.5.3 Value of information

The EVPI per patient was £0.19 (pre-frail) and £936.96 (frail) at the cost-effective threshold of £20,000. When scaling to the population level, the population EVPI were £6,626.32 (pre-frail) and £32,428,126.91 (frail) at the cost-effective threshold of £20,000 (Figure 7.4). The population EVPI increased to a local maximum (£46,965,305.12) at the point where the cost-effective threshold value at £17,000 for frail patients.

Figure 7.4. Population expected value of perfect information for pre-frail and frail patients



7.6 Discussion

The findings of this CEA indicated that surgery is a dominant strategy for pre-frail older patients aged ≥ 70 years; however, for frail patients, PET is a potentially cost-effective strategy. The finding that PET was a cost-effective strategy for frail older patients was in line with the clinical suggestions from the European Society of Breast Cancer Specialists (EUSOMA) and the International Society of Geriatric Oncology (SIOG) [12]. Moreover, according to high EVPI values of about £32 million (for frail patients) at the cost-effective threshold of £20,000, there will be great value in conducting more relevant research informing future economic evidence of PET versus surgery in frail older patients.

Interestingly, this Chapter found an opposite direction of incremental life year gained (0.26) and incremental QALYs gained (-0.11) comparing PET with surgery. One possible explanation is based on the assumption that patients receiving PET might develop a progression state with lower health utility values quicker than patients receiving surgery who might stay longer in the stable state with higher health utility values. The previous RCTs and meta-analyses have proved the explanation based on such an assumption [94]: patients receiving surgery had better progression-free survival than patients receiving PET despite a similar overall survival of the two treatments. Therefore, selecting life-year gained or QALYs gained as the outcome measures in decision-making is critical. Life-years gained or QALYs gained are approved as the recommended economic evaluation outcomes in different jurisdictions may produce opposite decision-making. According to the NICE guidance in the UK [83] and global consensus by ISPOR [189], QALY is suggested to be a standardised outcome measure for economic evaluations involving the quality and length of life gained by alternative technologies. Once choosing life-years gained as the outcome measure in decision-making, the quality of life gained for the alternative technologies may neglect.

The findings of this Chapter are consistent with the results from a previous cost-effectiveness analysis of surgery with adjuvant endocrine therapy versus PET for UK women aged ≥ 70 years by Holmes *et al.* (2021) [199]. In the CEA by Holmes *et al.* (2021) [199], the cost-effectiveness between surgery and PET was analysed by different age groups and levels of CCI. The results showed that PET is a cost-effective strategy compared with surgery for older patients aged $\geqslant$ 90 years, irrespective of CCI levels (76% of probability that PET is a cost-effective strategy at a CE threshold of £20,000). However, Holmes *et al.* (2021) [199] did not perform the value of information analysis.

The value of information analysis (VOI) is a powerful technique to inform the prioritisation of future research, as in Chapter 2 (Section 2.2.5). EVPI is the simplest way to quantify the upper bound of the uncertainty to prioritise future studies. The population EVPI estimated by this CEA was large for frail patients (£25,047,932.75) at the CE threshold of £20,000. This large population, EVPI for frail patients, suggested future prospective research would likely be valuable for the NHS based on this model-based CEA. The population EVPI represents the upper bound for the value that could be gained from further research [86]. The population EVPI was higher than £1.48 million. It was estimated as an empirical threshold value to inform whether future research would be of value or not, according to a systematic review by Thorn *et al*. (2016) [171]. The higher population EVPI may attract more favourable recommendations for research but not sufficient conditions for advising further research [171].

Meanwhile, the cost for previous research projects in England funded by public resources has been lower than this estimated EVPI. In general, the 3-year cost of £1-1.5 million awards of research can be provided by the NIHR Programme Grants for Applied Research [355]. Therefore, it is valuable for NHS England and health researchers to fund or conduct more research for older patients who are unfit for surgery (pre-frail or frail).

This study has some limitations that should be considered when interpreting the results. First, we did not consider the immediate mortality risk of surgery for frail patients who died during the surgical procedure. The frail patients had a higher proportion of death from surgery or suffering from post-surgical complications, leading to fewer LYs gained and higher costs for the patients with surgery. However, the surgeons will comprehensively assess the surgical feasibility to minimise such post-surgical complications and mortality risk. Thus, this limitation may not change the results.

Second, the transition probability from progressed to dead states was extracted from an RCT that assessed the survival outcomes for operable older women with better physical conditions. The results of the cost-effectiveness of surgery may be overestimated due to the higher cost and longer survival time of the progressed state for the patients with PET. According to the sensitivity analysis, this limitation of survival estimates of progressed to dead states will not change the results.

Finally, as there is a lack of evidence to evaluate the health-related quality of life (for example, utility values) for patients receiving PET due to frailty, this study used the multiplicative method to adjust utility values for frail patients. The disutility multiplier was estimated from a cohort study that focused on the utility values in older patients aged ≥ 65 years with cardiovascular disease stratified by frailty levels. Although these values were not fully translatable to the patients with breast cancer, the adjusted approach was used to reflect the loss of quality of life for frailty patients to diminish the impacts. Previous evidence (Chapter 3) elucidated that using the appropriate method to adjust utility values to fit the target population is a typical approach in model-based economic evaluations. This will not change the decision-making.

In the future, sub-group analysis for frail patients (for example, age subgroup of 70-, 75-, 80-, 85-, and 90+ years) to further inform the most optimal age group receiving PET as

a relatively cost-effective strategy. In addition, although this CEA provided an overall upper bound of cost for uncertainty to inform future studies and research funding, there will be more VOI techniques, for example, the expected value of partially perfect information, the expected net monetary benefit of sampling to design studies that maximise health benefits based on the one-way sensitivity analysis (tornado diagram Figure 7.1). Robust clinical evidence is needed to provide the probabilities from stable to progression or metastasis. Individual patients' hospital records can be used as the potential data source to evaluate the time to progression or metastasis in frail older patients due to comprehensive and accurate records of progressed or metastatic events for breast cancer.

7.7 Conclusion

Frailty-associated life expectancy is crucial in influencing the cost-effectiveness of PET versus surgery in older women aged ≥70 with ER+ early-stage breast cancer. Based on the thesis findings, surgery is the dominant strategy for pre-frail patients, while for frail patients, PET is a cost-effective strategy with lower costs and higher health-gain. The relative cost-effectiveness of surgery reduces progressively as the patient's physical functioning gets frailer and frailer, and there is still significant uncertainty about the current results. Consequently, there is a high value in conducting more studies on frail older patients. In the future, the values of the study of PET versus surgery in older patients should focus on specific frail patients.

Chapter 8 Discussion and conclusion

This chapter reports the main findings (Section 8.1), strengths and limitations of the work presented in the thesis (Section 8.2), future research (Section 8.3), and conclusions drawn by the thesis (Section 8.4).

8.1 Main findings

The highlight of this thesis was the generation of economic evidence (cost-effectiveness) comparing PET with surgery for older women with ER+ early-stage breast cancer stratified by levels of frailty. Research aims were progressively studied by applying specific methods, including systematic reviews (Chapters 3 and 4), decision analytic modelling (Chapters 5 and 7), matched cohort study, and cohort study (Chapters 6). The main findings of each chapter potentially contribute to facilitating the clinical decision-making of patients and healthcare professionals, informing policy decision-makers of optimising clinical guideline healthcare resource allocation, and supporting researchers for future healthcare research.

This thesis adopted the NHS perspective for the cost-effectiveness analysis to generate economic evidence that can inform the NICE clinical guidelines to select the cost-effective treatment strategy for patients living in England. Furthermore, the economic evidence (e.g., EVPIM and EVPI) generated in this thesis provided more practical values for healthcare authorities regarding implementation decisions and the need for further research. Moreover, this thesis compared clinical evidence (survival benefits) between PET and surgery stratified by levels of frailty and comorbidity; the result can facilitate clinical professionals in providing evidence-based treatment strategies to individual patients with corresponding physical functioning. Therefore, the findings optimise the evidence-based decision-making process for clinicians, patients, and policymakers in breast cancer management (recognised as shared decision-making).

8.1.1 Guideline and policy decision-makers

8.1.1.1 Contributions to the knowledge gap and implications

The critical contribution of this thesis is to evaluate the cost-effectiveness of PET versus surgery in older women with ER+ early-stage breast cancer at different levels of frailty. The results of the thesis are the essential evidence to facilitate and improve guideline formulation and update by healthcare policy authorities (that is, the NICE in England) because maximising population health is the fundamental mandate of the NICE under the prevailing budget constraint for healthcare through efficiently allocating resources.

This thesis assessed the cost-effectiveness of PET versus surgery in older patients by three levels of physical functioning. PET is not a cost-effective strategy compared with surgery for older patients who are fit for surgery (Chapter 5). Meanwhile, the thesis also quantified the health forgone from PET under the current surgical rate for older patients who are fit for surgery through the value of implementation analysis. This finding of the value of implementation analysis can inform the health authorities to strengthen the NICE guideline adoption and increase the surgery rate for patients who are physically fit for surgery. The findings can also inform and communicate with patients who are fit for surgery about the health benefit/forgone from surgery or PET, which can help to encourage surgery uptake as first-line treatment in routine clinical practice to maximise population health benefits.

Moreover, for patients who are potentially unfit for surgery (Chapter 7), PET is a potentially cost-effective strategy for frail patients but not for pre-frail patients. In addition, quantifying the uncertainty based on the current information makes it valuable for healthcare authorities and research funders in England to conduct further research in the future to diminish the uncertainty. The findings of the thesis inform policy-decision makers to improve the healthcare strategies formulation to maximise the health benefits at a population level and efficiently allocate the healthcare resource in England.

8.1.1.2 Discussion of key findings

Similarly, one should be cautious in applying the thesis findings to policy decision-making. Uncertainty is inherent in any decision for relative cost-effectiveness and is a crucial influence on the decision-making process at the NICE guidance [133, 153]. Based on the three types of uncertainty [154], the thesis may have a minor influence on methodological uncertainty because the thesis followed the NICE reference case to develop the model-based economic evaluation. For the structural uncertainty, in the Markov model, three health states were included (stable, progressed, and dead), which is in line with the findings of the systematic review (Chapter 3) that the three states Markov model were the main model structure for model-based economic evaluations for older women with breast cancer. Thus, the structural uncertainty of the model structure in the thesis may not significantly influence decision-making.

Finally, although surgery was found as a cost-effective strategy for the pre-patients who are fit for surgery and pre-frail in this thesis, the sensitivity analysis shows PET was a potentially cost-effective strategy for frail patients, considering parameter uncertainty in the models. Overall survival is the key factor and driver for the cost-effectiveness of decision-making to estimate the transition probability to the dead from stable or progressed states, which aligns with the clinical suggestion [356]. PET is suggested for patients with an expected shorter life expectancy. Thus, the assessment of expected life expectancy may be a vital indicator of the cost-effectiveness of PET versus surgery for older patients.

From the previous analysis by Holmes *et al.* (2021) [199], the probability that surgery is cost-effective for the three levels of CCI ranged from 67% to 93% of older patients aged 70-79 years and from 54% to 91% of older patients aged 80-89 years at the CE threshold of £20,000 [199]. In the thesis, the probability that surgery is cost-effective was 88% and

38% for the pre-frail and frail patients aged ≥ 70 years, respectively, at the CE threshold of £20,000 (Chapter 7). The results had great uncertainty with population EVPI for pre-frail and frail patients were over £6.5 million and 30.2 million at the CE threshold of £20,000. It is valuable to conduct further evaluations on frail patients in maximising population health benefits for the NHS decision-making process in England.

8.1.2 Patient and healthcare professionals

8.1.2.1 Contributions to the knowledge gap and implications

Another contribution of this thesis is to quantify the clinical and comparative effectiveness of PET and surgery for older women with ER+ early-stage breast cancer, which is the critical basis for the clinical decisions made by healthcare professionals and patients. First, the clinical effectiveness based on the findings of the thesis indicated that surgery is the optimal treatment strategy with maximised overall survival benefits for older women with ER+ early-stage breast cancer who are fit for surgery or have a minor physical functioning issue.

Second, this thesis showed that surgery had superior overall survival to PET for patients who are fit for surgery or have a mild (pre-frail) or severe (frail) physical functioning issue. However, there were limited overall survival benefits gained from surgery compared to PET for frail patients, according to the no significant difference in the treatment effects of PET from surgery. The findings of this thesis can inform the clinical decision-making by healthcare service providers as an evidence-based reference and facilitate the patients to make the most appropriate clinical decision for themselves in treating ER+ early-stage breast cancer.

From a clinical perspective, the value of this thesis is using the well-designed study (Chapter 6) to generate evidence of the clinical decision-making for older women with ER+ early-stage breast cancer in terms of clinical effectiveness (overall survivals) and

comparative effectiveness between PET and surgery (breast cancer-specific mortality). Compared to previously published studies (described in Chapter 2, Section 2.4) on a similar topic, this thesis made patients receiving surgery or PET comparable (by using the propensity score technique) to estimate the overall survival by different primary treatments for older patients who are unfit for surgery due to frailty or comorbidity. Consequently, these results can inform healthcare service providers and patients of reliable quantitative data as evidence to support them in making the most appropriate clinical decisions according to the individual patient different physical functioning (i.e., frailty or comorbidity) levels.

Finally, the thesis results contribute to the broader evidence of breast cancer management. Current clinical breast cancer management guidelines only provide surgery as the primary prioritised strategy. There is a lack of feasible treatment strategies for patients with frail functioning in the guidelines. Thus, clinicians must provide frail patients with an appropriate treatment strategy based on their personal experience or consensus. This thesis quantified the survival benefits for older patients who received surgery or PET stratified by levels of comorbidities and frailty, which can be used as evidence to inform and assist patients in the most appropriate clinical decision-making. In addition, the results of this thesis can be used as evidence to optimise the current breast cancer survival "predict tool" [357]. This tool was developed by the University of Cambridge and the National Cancer Registration and Analysis Service to predict the average survival benefit of post-surgery based on the tumour's biological characteristics (e.g., age, menopausal status, the ER and HER2 status). According to routine clinical practice, a quarter of older women aged > 70 do not receive surgery as an initial treatment strategy. Consequently, the survivals benefits quantified in this thesis can supplement the "predict tool" to predict older patients who do not receive surgery, which can be used as a decision-making tool for patients and clinicians.

8.1.2.2 Discussion of key findings

The key challenge in applying findings that PET is an appropriate strategy for frail older patients in clinical practice is assessing the physical functioning to judge whether patients are fit for surgery. This thesis selected two leading proxy indicators, i.e., frailty and comorbidity, during the evaluation. These two factors were identified from previous observational studies associated with the treatment options in surgery or PET. Since the observational studies (Chapter 6) used secondary healthcare databases, including CPRD, HES, Cancer Registry and ONS death registration, frailty is not recorded as common assessment indexes, such as active daily living score (ADL) for frailty [358]. For the CCI estimation, some morbidities (e.g., diabetes mellitus with minor symptoms or minor hypertension may not be identified initially) or the morbidities over one year diagnosed may be missing during the estimation using primary and secondary healthcare datasets records in the thesis. This common situation happens as a natural limitation of secondary data; that is, databases may not record the specific variable required by the research question.

Nonetheless, this thesis used the hospital frailty risk score (HFRS) and Charlson Comorbidity Index (CCI) to characterise frailty and comorbidity [76, 325]. The algorithms of HFRS and CCI as estimators of frailty and comorbidity are developed to predict short-term (3-month) hospitalised-related mortality, re-admission rate and post-surgical complication rates, and long-term (5, or 10-year) all-cause mortality respectively, and validated using the UK population [76, 325]. Although these indicators, i.e., CCI and HFRS, may not entirely and comprehensively characterise whether patients are fit for surgery, they reflect the consideration of clinical decision-making for older patients who are unfit for surgery. Therefore, predicting the likelihood of receiving surgery or PET in clinical is feasible.

As a commonly accepted index to indicate long-term mortality, CCI is widely used in many research studies to predict mortality or indicate clinical decision-making [359-362]. This thesis follows suggestions and comments on previous studies to use three levels of CCI indicators of clinical and comparative effectiveness to inform clinical decision-making [79, 290, 351, 363, 364]. In addition, as mentioned in Chapter 2 (Section 2.), although there is no clear definition of frailty in clinical, frailty has been widely used as a critical indicator in clinical decision-making, particularly in surgical procedures.

Many algorithms and scales have been developed to quantify frailty and inform clinical decision-making. A scoping review systematically summarised the currently used measurement of frailty for older patients aged ≥ 65 years worldwide [365]. The review results indicated that 29 different frailty measurements are generally used to predict the prognosis of specific diseases [365]. The older population as a specific group are the target population for frailty measurement in clinical decision-making that facilitates healthcare service provider to judge whether patients tolerate highly intensive or invasive treatments, e.g., surgical procedures for cancer, cardiovascular disease etc. [365].

For older patients with cancer, the comprehensive geriatric assessment (CGA) is a highly recommended frailty assessment strategy for geriatric oncologists worldwide and the NICE guideline in England [365-368]. According to the International Society of Geriatric Oncology Consensus on Geriatric Assessment in Older Patients with Cancer [367], eight domains should be comprehensively assessed for older patients with cancer, including functional status, comorbidity, cognition, mental health status, fatigue, social status and support, nutrition, and presence of geriatric syndromes. The results of CGA can facilitate the healthcare service providers to characterise the physical functioning of older patients comprehensively and accurately with cancer to inform patients of the most appropriate and individualised treatment strategy.

In England, the NICE guideline also suggested using CGA to assess older people with complex needs from hospital admission [368]. Understanding complex needs may involve complex medical, functional, psychological and social needs, which may lead to receiving a non-standard treatment strategy [368]. Overall, although clinical decision-making for older patients unfit for surgery may not be comprehensively characterised using HFRS or CCI, it is still valuable to inform clinical decision-making based on the current information.

8.2 Strengths and limitations of the work presented in the thesis

The specific strength and limitations of systematic reviews (Chapters 3 and 4), model-based evaluation (Chapters 5 and 7) and observational study (Chapter 6) in the thesis were presented within their respective chapters and are not repeated here. However, two potential broader limitations to the thesis, related to treatment optimisation based on share-decision making (Section 8.3.1) and the omission of non-health benefits (Section 8.3.2), are now discussed.

8.2.1 Strengths of the work presented in the thesis

The thesis had relative strength in generating clinical and economic evidence for older women with ER+ early-stage breast cancer. First, the thesis used a mixed method progressively address the research questions. Initially, systematic reviews were used to summarise the current evidence and knowledge to inform the study design. Systematic reviews were conducted to summarise the current evidence in comprehensively identifying the study's strengths and limitations to inform the thesis's study design. The NICE guidance in the decision-making process recommends a systematic review. Therefore, this thesis uses systematic reviews to summarise the evidence (Chapter 3) and inform the subsequent research (Chapters 4 to 7).

This thesis provided a comprehensive assessment of the cost-effectiveness of PET compared with surgery for older patients by levels of frailty to inform decision-making. Compared to a previously published CEA for older women with early-stage breast cancer by Holmes et al. (2021) [199], three advantages of this thesis (Chapter 5 and Chapter 7) can be identified. Firstly, this thesis used two survival functions to estimate the probabilities from stable to progression and death, and this estimation approach can quantify the survival benefit of surgery and PET varying with time, which can reflect the clinical effectiveness of PET and surgery more closely to reality. This estimation approach can minimise the bias from clinical effectiveness influenced by time. Secondly, this thesis analysed the cost-effectiveness of PET compared to surgery by HFRS levels. In contrast, Holmes et al.'s CEA evaluated the cost-effectiveness of PET compared to surgery by levels of the CCI [199]. As discussed in Chapter 6, the CCI and HFRS reflect different outcomes for geriatrics assessment, of which the CCI reflect the long-term mortality (i.e., ten years mortality). HFRS reflects the short-term consequences (i.e., 30-day mortality, extended hospital-stay (> ten days in hospital), and emergency readmission within 30 days of discharge). Therefore, this thesis can supplement current economic evidence of surgery and PET used in older women with early-stage breast cancer.

Thirdly, compared to the CEA by Holmes, this thesis additionally conducted the value of implementation analysis (Chapter 5) and the value of information analysis (Chapter 7). The study by Holmes et al. (2021) [199] and this thesis (Chapter 5) indicated that surgery is cost-effective for patients who are physically fit for surgery. However, this thesis further quantified the health forgone for patients who are fit for surgery according to the current routine clinical practice, which can support the healthcare authorities to optimise their breast cancer management actions in the future. Although based on the current clinical evidence, PET is a cost-effective strategy for frail older women (Chapter 7). However, the quality of evidence for the comparative clinical effectiveness of PET compared to

surgery in treating older women with breast cancer still needs to improve. Chapter 7 additionally quantified the current uncertainty presented by EVPI to inform the healthcare authorities of the values of future research (Chapter 7).

Furthermore, large, longitudinal linkage data were used to perform a cohort study of patients with breast cancer to estimate the overall survivals of PET and surgery with control of the selection bias. This thesis used the cancer registry linked to other high-quality data sources, such as CPRD, HES and ONS death, to maximise the sample size and to comprehensively assess the clinical and comparative effectiveness. The cancer registry is considered a high-quality data source in England that comprehensively records citizens diagnosed with cancer. Therefore, in this thesis, the observational data provided reliable survivals with the adjustment of the selection bias of PET for older patients to inform the further economic evaluation.

Simultaneously, in clinical practice, due to the service provision capacity, particularly in the post-COIVD era, surgery may not be the first-line treatment for older patients who are fit for surgery for different reasons, as national audits in England reported. Thus, the implementation analysis's value was initially used to inform the healthcare policy formulation and update to maximise the population's health benefit.

8.2.2 Limitations of the work presented in the thesis

The findings of the thesis still need to be investigated in the reflection of patients and clinicians to supplement current evidence further to inform clinical decision-making. Evidence-based information is the basis for the shared decision-making between patients and healthcare professionals. However, treatment decided by patients or clinicians may consider more information. The current results of the thesis only provided the survival outcomes between surgery and PET by levels of physical functioning indicated by frailty and comorbidity. Further research is necessary to understand whether

the results will guide the clinical decision-making appropriately or whether other potential factors may affect the treatment selection.

Another limitation is the prevailing paradigm for the economic evaluation of health technologies in England was concerned with the maximisation of population health only [86, 123-126]. Each treatment in the thesis would provide potential benefits to patients with specific characteristics. For example, PET or surgery, in general, is provided to the patient according to their physical functioning. However, there is still a group of patients with breast cancer with the challenge of clinical decision-making due to other potential reasons, such as triple-negative breast cancer (ER-, PR- and HER-) [369], ductal carcinoma in situ (DCIS) [370], and locally advanced or metastatic breast cancer [371]. Therefore, although the thesis findings can be applied to most older women with breast cancer, the generalisability of the findings to the population level of patients with breast cancer is still a limitation when applying the findings of the thesis.

In addition, the limitations of using QALYs as a measure to frame the health consequences of alternative strategies were not unique to this thesis. Health utility values as a weight of quality of life were used to estimate the QALYs and can be measured by different methods [86, 135-137]. EQ-5D is the most commonly used and approved multiple-dimensional instrument that may not adequately reflect the health benefit for specific diseases (e.g., aural or visual problems or mental disorders) [372], and broader outcome measures can be utilised in the evaluation of the public health interventions [373, 374]. Well-being and capability (e.g., life and psychological satisfaction) are more considered when older patients decide on clinical treatment between surgery or PET rather than only the clinical effects [375, 376].

According to the survey on postmenopausal women with early-stage breast cancer, older women would pay more attention to the post-treatment influence if surgery provided

limited benefits, such as the influence of typical daily life and psychological well-being [71, 81]. Therefore, there may potentially be other health benefits (e.g., life and psychological satisfaction) that were not measured by the EQ-5D instrument.

8.3 Future study

Several questions are valued to be addressed in future research simulated by the findings of this thesis and their respective limitations. This section summarised the proposed research aim and objectives for future research.

The results of Chapter 4 suggested that there is a lack of studies evaluating the health state utility values for the older population, particularly for patients with breast cancer receiving non-surgery as the initial treatment strategy. Only one study was conducted for older women with breast cancer receiving surgery and non-surgery initial treatment strategies [363], and the health state utility values of this study were measured by EQ-5D-5L UK tariff [260]. However, the NICE does not recommend using EQ-5D-5L UK tariff as the data source to estimate the health states utility values for the economic evaluations due to concerning the quality and reliability of the data collected in the valuation study, and the methods used to model these data for EQ-5D-5L value set for England [377]. Therefore, due to the ageing population issue, more studies, for example, questionnaires or observational studies for older populations or their health carer, are needed to be conducted to measure the health state utility values for the older population and such non-standardised treatment strategies (i.e., surgery).

Moreover, as discussed in the limitations in Chapter 6, some covariates, such as tumour characteristics, physical functioning measures (e.g., falling down risk, polypharmacy, and medication adherence), patient preference, and psychological wellbeing for older patients, were not included to estimate the survival benefits between surgery and PET. These covariates may potentially influence the survival benefits estimation. Therefore, a

prospective cohort study can be conducted to collect such variables to estimate the outcomes more accurately. In addition, progression-free (or disease-free) survival for patients taking PET or surgery are the key drivers influencing the life-years gained, and QALY gained (discussed in Chapter 7). Given that progression of breast cancer is confirmed by image data (Ultrasound test or Computed Tomography scanning) rather than the routine reimbursement data or registry data, and thus a cohort study using hospital records may be a possible way to estimate the progression-free and disease-free survivals in the future.

Furthermore, as discussed in Chapter 7, the studies by Holmes et al. (2021) [199] and this thesis indicated that PET is a cost-effective strategy for older women who may not receive surgery as the initial treatment strategy. Holmes et al. also stratified the analyses by lymph node status, levels of CCI, and age groups (e.g., 70-80 years, 80-90 years and 90+ years) and found that for women aged $\geqslant$ 90 years, no matter the CCI and lymph node status, PET is a cost-effective strategy [199]. Meanwhile, according to the discussion in Chapter 6, different strengths of ER positivity will influence the treatment effects of PET. Therefore, it would be interesting to further analyse the cost-effectiveness of PET compared to surgery by age groups (e.g., 70-80 years; 80-90 years and 90+ years) and strengths of ER positivity using the data in Chapter 7. In addition, due to the high EVPI quantified in Chapter 7, additional economic evaluations must be conducted to assess the cost-effectiveness of PET compared to surgery for older patients who are unfit for surgery.

Based on current clinical and economic evidence and a broader limitation of the thesis that this thesis did not have any patient and public involvement and stakeholder engagement, as described in Section 8.2.2, a subsequent research programme investigating treatment preference between surgery and PET in older patients is necessary to understand the issues of health care the medication use. A discrete choice

experiment (DCE) can be used to understand individuals' preferences and decision-making processes by setting a series of hypothetical scenarios or choice sets, which can inform patients, the public, and stakeholders to help make informed choices and decisions [378]. Given that patient preference is a key influential factor in shared decision-making, there is another critical point on whether older patients will change their decision-making based on the current clinical and economic evidence generated in this thesis. A relevant topic for future research was investigating the treatment preference of older patients and the clinician's advice and providing more valuable information to conceptualise the decision problem (i.e., include more information during the future study to inform decision-making).

8.4 Conclusion

In line with the national guideline, PET is not a cost-effective strategy compared with surgery for older patients who are physically fit for surgery or have mild-moderate frailty, and surgery should be encouraged for patients with good physical functioning to reduce the health forgone by PET implementation. In comparison, PET is a potentially cost-effective strategy for frail older patients. Surgery provides maximised clinical and cost-effectiveness as the first-line treatment for patients who are physically fit or minor-to-moderate frail. The economic and clinical evidence can inform healthcare policymakers to encourage surgery uptake for operable patients to minimise the health foregone. For frail older patients unfit for surgery, although PET is a potentially cost-effective strategy according to the current results, clinical and policy decision-makers should be cautious when recommending PET as the primary treatment strategy due to the uncertainty in the results with a high EVPI result. In addition, this thesis also supported the researchers and funders in developing further studies specifically for the frail population to minimise the decision uncertainty and maximise the health benefits, which were deemed potentially valuable to the NHS.

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Appendices

Appendix 1. Full strategy to disseminate research

Full strategy to disseminate research

This appendix reports the proposed publication strategy to disseminate the research presented in this thesis. Five clear outputs are described in terms of their (1) proposed title; (2) the relevant section from the thesis; and (3) a description of the manuscript.

Publication 1:

Title: Systematic review of the evidence sources applied to cost-effectiveness analyses for older women with primary breast cancer

Relevant Section from Thesis: Chapter 3

Description: A systematic review of model-based economic evaluations in older women with early-stage breast cancer was reported in Chapter 3. This review appraised current evidence sources to estimate input parameters used in model-based economic evaluations in postmenopausal women with primary breast cancer, and published in Cost Effectiveness and Resource Allocation in March 2022 as the initial output from this thesis.

Publication 2:

Title: The Impact of Age on Health Utility Values for Older Women with Early-stage Breast Cancer: A Systematic Review and Meta-regression

Relevant Section from Thesis: Chapter 4

Description: Another systematic review of the studies measuring health state utility values for postmenopausal women with early-stage breast cancer was reported in Chapter 4. This review estimated health state utility values of women with breast cancer and their correlation with age. Results of these systematic reviews were used to inform

subsequent economic evaluations and published in Health and Quality of Life Outcomes in December 2022.

Publication 3

Title: Health Loss from Primary Endocrine Therapy in Older Women with Operable Early-stage Breast Cancer: A Cost-effectiveness and Value of Implementation Analysis

Relevant Section from Thesis: Chapter 5

Description: A model-based cost-effectiveness analysis and value of implementation analysis were conducted based on randomised control trials to model the cost-effectiveness of PET versus surgery in older women with early-stage breast cancer “fit for surgery”. The results quantified England's health and economic loss associated with the imperfect implementation of guidance, i.e., using PET instead of surgery.

Relevant Audience: Healthcare professionals, health economists, and related healthcare policymakers.

Target Journal: This study had specific relevance to breast cancer management in England. Therefore, the most suitable target journal for the manuscript was the European Journal of Cancer, which is the official journal of the European Organisation for Research and Treatment of Cancer (EORTC) and the European Society of Breast Cancer Specialists (EUSOMA).

Publication 4

Title: Survival of Early-stage Breast Cancer in Postmenopausal Women Receiving Surgery versus Primary Endocrine Therapy

Description: The impact of frailty on clinical effectiveness was investigated in a cohort study using a large datalink in the UK, including CPRD, HES, Cancer Registration, ONS Death Registration, and patient-level Index of Multiple Deprivation. Mortality and survival were measured in younger (50-69 years) and older (70+ years) postmenopausal women

with early-stage breast cancer stratified by the degrees of frailty. There was no statistical significance of 10-year overall survival between surgery and PET in patient at an older age. The risks of all-cause and breast cancer-specific mortality of PET were reduced compared to surgery with increase in the level of frailty.

Relevant Audience: Healthcare professionals, and researchers interested in breast cancer.

Target Journal: This study had specific relevance to breast cancer management in older patients in England. Therefore, the most suitable target journal for the manuscript was the PLOS Medicine, which focus on the studies on diseases and risk factors that cause the greatest burden worldwide based on the evidence-based approach.

Publication 5

Title: Cost-effectiveness Analyses of Primary Endocrine Therapy in Older Women with Early-stage Breast Cancer by Levels of Frailty

Relevant Section from Thesis: Chapter 7

Description: A model-based cost-effectiveness analysis and value of information analysis compared PET versus surgery in older women with early-stage breast cancer who are “frail and potentially unfit for surgery”. Although surgery is a cost-effective strategy, PET is potentially cost-effective for older women who are unfit for surgery due to frailty, albeit with a notable uncertainty. The upper bound of cost to diminish the uncertainty has also been identified in this study.

Relevant Audience: Healthcare professionals, health economists, and related healthcare policymakers.

Target Journal: This study had specific relevance to breast cancer management and future research of breast cancer in older patients in England. Therefore, the most suitable target journal for the manuscript was the PharmacoEconomics, which is

dedicated to the clear communication of complex pharmacoeconomic issues related to all healthcare interventions.

Appendix 2. Description of three types of decision analytic model

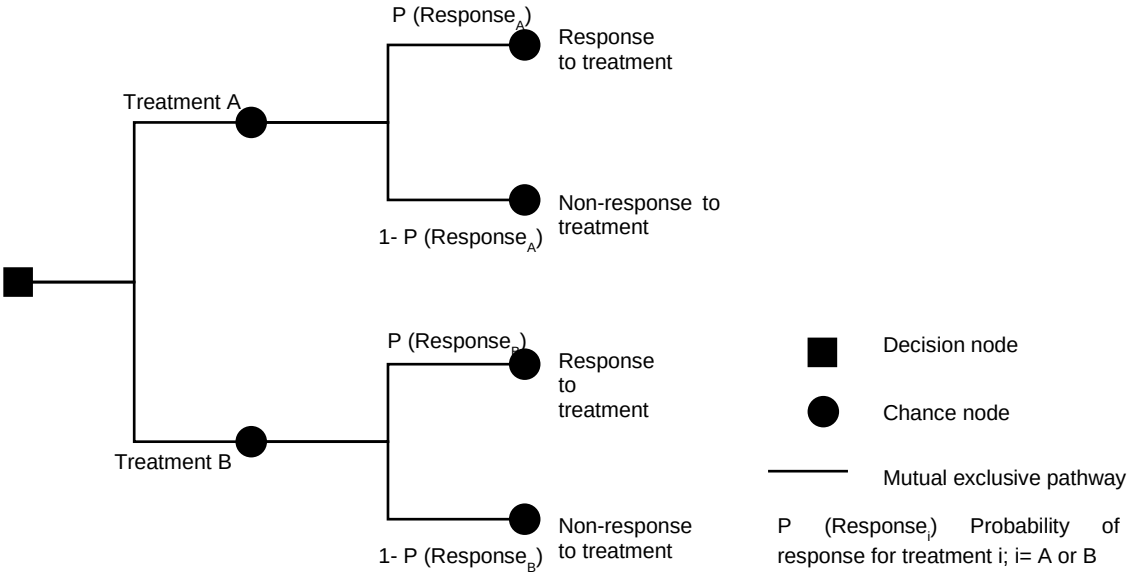
This appendix describes three typical decision-analytical models i.e., decision-tree, Markov model and discrete event simulation. These three types of decision-analytical models can be used in a model-based economic evaluation to estimate the expected cost and health outcomes associated with various comparator health technologies. Different types of models selected in the economic evaluation can be used to address different decision problems by various approaches to estimate the expected outcomes. The following section explains the key design features, advantages, and disadvantages.

A2.1 Decision tree

A decision tree represents a decision and subsequent events that may occur to patients over time. The decision tree is a flowchart-like structure that includes three key elements as the figure show (Figure A2.1) (1) the decision node (depicted as a solid square); (2) the chance node (depicted as a solid circle); (3) the branch is a flow link between the decision node and chance nodes (depicted as a solid line) [1]. Each branch forms mutually exclusive pathways that are the patient mutually exclusive pathway following the decision [2]. The terminal node that represents the interest outcomes (e.g., QALY, costs) is attached to the end of each pathway. Each pathway including the decision and chance events assigns an occurred probability that can be identified from clinical literature.

The expected cost and QALYs in each branch of the decision tree can calculate an analytical solution [3]. The probability in a mutually exclusive branch can be estimated using conditional probability which is to multiply the probabilities associated with each chance event along that pathway [1]. The expected outcomes of a specific treatment alternative can finally be estimated by summing the expected outcomes of each mutually exclusive pathway associated with that treatment.

Figure A2.1 Illustrative example of a decision tree



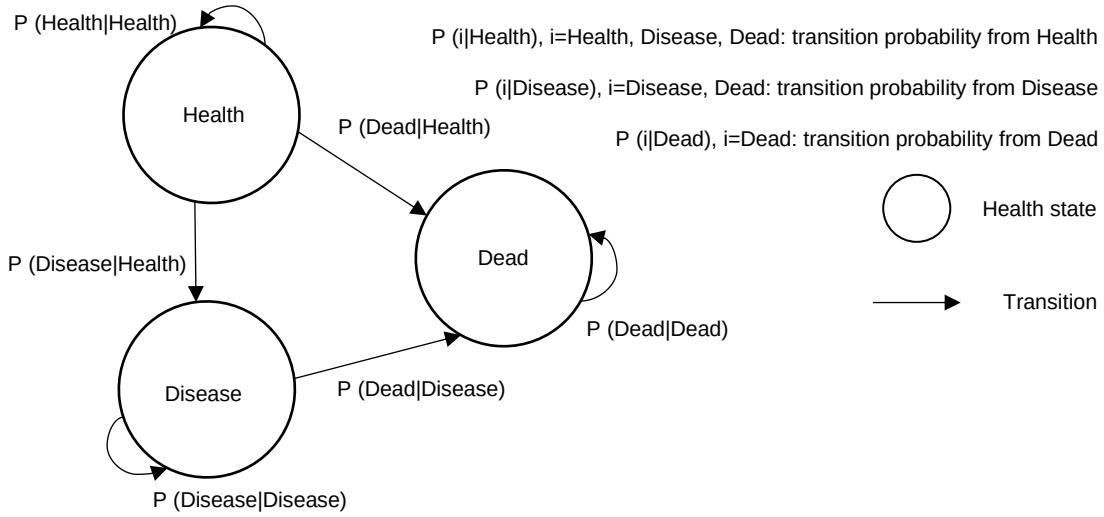
The principal merit of the decision tree is relatively simple to build and comprehend. However, there are also noticeable drawbacks. First, the workload of calculating the analytical solutions would exponentially increase and be difficult to handle as the number of mutually exclusive pathways increases [4]. Second, as the key limitation, the decision tree assumes all the outcomes occur simultaneously given that the expected outcomes are estimated analytically. This may not be appropriate and justifiable for chronic conditions. Therefore, it is difficult to characterise the clinical events that occurred over time (particularly lifelong) using a decision tree [5].

A2.2 Markov model

Markov model is a typical states transition model, which represents patient moves between mutually exclusive health states over time (Figure A2. 2) [6]. The Markov model is characterised by three key elements: (1) A finite set of mutually exclusive health states relevant to the decision problem, which reflect the natural history of the disease [7]. Patients must belong to one of the health states at any time point [7]. (2) Transition probabilities moving between states per unit of time. The transition probabilities from one

state to another must sum to 1. (3) Time, which is divided into discrete cycles of equal length [4].

Figure A2. 2. Illustrative example of Markov model



A cohort of identical patients between health states over time is simulated to estimate the expected QALYs and costs associated with alternative strategies. QALYs and costs are assigned to the defined health state [4]. A cumulative QALYs and costs were estimated according to the duration of each patient accrued in each health state. The expected outcome is estimated by dividing the total outcomes by the number of patients simulated in the cohort.

The advantage of the Markov model is to take time into account, which would incorporate the different clinical events (recurrence or progression) into analysis. Also, Markov model still has three potential limitations. First, Markov models are characterised by the Markovian assumption that assumes that the probability of transitioning between health states depends only on the current health state. The practical implication of the assumption is that the transition probabilities only depended on the current health state regardless of previous health states (i.e., Markov model does not have memory

regarding the historic health states that patients occupied) [4, 7]. This assumption meant the clinical event may not be impacted by the previously experienced event. Second, patients can only localise in one health state at a time. Second, patients can only localise in one health state at a time. This may need many states to characterise the progression of disease, and also some assumptions with respect to the selection of health state [8]. Finally, each cycle in the analysis is an equal discrete length of time, and this may not be realistic in the real world. Patients will experience a defined health state in a continuous time, instead of a discrete-time duration. Therefore, a half-cycle correction can be applied to adjust results by assuming transitions occur half-way through each cycle [4, 7].

A2.3 Discrete event simulation

A discrete event simulation (DES) represents the experience of specific events that occurred to individual patients over time, which evaluates the level of an individual patient [2].

There are four key elements to characterise the model design: (1): entities, entities are the objects to be modelling experience events over time (conventionally defined as the patient) [9]. (2) attributes are the specific characteristics to define the entities (e.g., age, and sex) [9]. (3) events are characterised as something interested in that happened to a patient over time [9]. (4) time is advanced in a DES model according to when the next event is scheduled to occur [9].

DEC models estimate the expected QALYs and cost by simulating a cohort of patients over a predefined period of time. A DEC starts from a single patient entering the model, the attributes of the patients are sampled from representatives of a wider population. The patients' time of specific events are identified from survival curves using time-to-event data, which can be update if necessary [10]. The events time ordered by ascending, and

patients experienced the events subsequentially. The patient costs and QALYs can be extracted and stored as attributes over time. Each patient in the cohort repeats this process until all patients in the cohort have been simulated through DES. The expected cost and QALYs can be estimated finally similar to the Markov model, by dividing the total cost and QALYs by the number of patients in the cohort.

The advantage of DES is that model can remember the history of each simulated patient by storing information within the patient-level attributes [11]. It is valuable that remember the history of all patients in the cohort, if the subsequential event would be impacted by the previously historic events. However, this model required high computational demanding, which may need thousands of patients to estimate the results [11]. Besides, PSA also needs a great amount of calculation. In addition, time-to-event data is a key message to run the simulation, and insufficient time-to-event data may limit the model's use [8].

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Appendix 3. Chapter 3: Publication version of Chapter 3

This appendix reported the published version of the systematic review for the full-economic evaluation of older women aged ⩾ 70 years with early-stage breast cancer. The systematic review was published in *Cost Effectiveness and Resource Allocation* in March 2022.

The appropriate citation for the study is:

- Wang Y, Gavan SP, Steinke D, Cheung KL, Chen LC. Systematic review of the evidence sources applied to cost-effectiveness analyses for older women with primary breast cancer. Cost Effectiveness and Resource Allocation. 2022;20(1):9.

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Cost Effectiveness and Resource Allocation

REVIEW Open Access

Systematic review of the evidence sources applied to cost-effectiveness analyses for older women with primary breast cancer

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Abstract

Objective: To appraise the sources of evidence and methods to estimate input parameter values in decision-analytic model-based cost-effectiveness analyses of treatments for primary breast cancer (PBC) in older patients (≥ 70 years old).

Methods: Two electronic databases (Ovid Medline, Ovid EMBASE) were searched (inception until 5 September-2021) to identify model-based full economic evaluations of treatments for older women with PBC as part of their base-case target population or age-subgroup analysis. Data sources and methods to estimate four types of input parameters including health-related quality of life (HRQoL); natural history; treatment effect; resource use were extracted and appraised. Quality assessment was completed by reference to the Consolidated Health Economic Evaluation Reporting Standards.

Results: Seven model-based economic evaluations were included (older patients as part of their base-case (n = 3) or subgroup (n = 4) analysis). Data from younger patients (< 70 years) were used frequently to estimate input parameters. Different methods were adopted to adjust these estimates for an older population (HRQoL: disutility multipliers, additive utility decrements; Natural history: calibration of absolute values, one-way sensitivity analyses; Treatment effect: observational data analysis, age-specific behavioural parameters, plausible scenario analyses; Resource use: matched control observational data analysis, age-dependent follow-up costs).

Conclusion: Improving estimated input parameters for older PBC patients will improve estimates of cost-effectiveness, decision uncertainty, and the value of further research. The methods reported in this review can inform future cost-effectiveness analyses to overcome data challenges for this population. A better understanding of the value of treatments for these patients will improve population health outcomes, clinical decision-making, and resource allocation decisions.

Keywords: Economic evaluation, Decision-analytic modelling, Data sources of input parameters, Older women, Primary breast cancer

Introduction

Around half of the deaths from cancer occur in patients older than 70 years of age [1]. Breast cancer is the most prevalent cancer for females, and older patients may have different treatment goals than a younger population [2]. The increased likelihood of long-term comorbidities and frailty in this older population may preclude conventional treatment strategies (such as first-line surgery

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or adjuvant chemotherapy) due to the increased risk of treatment-related adverse events compared with younger people [3]. As a consequence, clinicians and decision-makers may be uncertain about the most appropriate way to manage these older patients [4]. Health economic evidence can inform treatment recommendations for breast cancer in older patients by comparing the incremental cost and health outcomes associated with different strategies available for this population [5]. However, robust evidence for the relative cost-effectiveness of the various treatment strategies observed in routine practice for older patients with breast cancer, including non-surgical intervention, is currently sparse.

Decision-analytic models are essential to produce this cost-effectiveness evidence by synthesising all relevant evidence and extrapolating expected cost and health outcomes over a lifetime time horizon [6]. As a minimum, health states such as 'disease-free', 'recurrence' (or 'progressed disease'), and 'dead' have been used previously to develop the structure of decision-analytic models for breast cancer [7]. This structural characterisation of disease is unlikely to vary by the age of diagnosis. However, there are few sources of evidence derived from older patients to populate the input parameter values of these decision-analytic models. The majority of randomised controlled trials (RCTs) of treatments for breast cancer, for example, have either excluded older patients due to their higher risk of morbidity and mortality or have recruited relatively low numbers of older patients [8]. Therefore, in the absence of data from older patients to populate key input parameter values, indirect evidence sourced from younger patients may be used instead to help estimate the cost-effectiveness of different treatment strategies for primary breast cancer in an older population.

Potential challenges may arise by using indirect evidence from younger patients if there are systematic differences with older patients in, for example, resource use, health-related quality of life (HRQoL), the natural history of the disease, or treatment benefits and harms. Older patients with breast cancer may have more interactions with the health care system and consume greater quantities of health care resources post-treatment than younger patients because of their relatively higher likelihood of comorbidity and frailty. Similarly, age-related comorbidities may result in older patients having relatively lower health-state utility values than younger patients [9]. The natural history of the disease may vary between younger and older patients if prognostic factors (such as endocrine receptor positivity) differ across age groups [10]. The magnitude and duration of benefit or direct harm from treatment (for example, the severity of adverse events after receiving chemotherapy) will likely depend on frailty experienced to a greater extent by older patients than younger patients [11].

In light of these potential differences between older and younger patients with primary breast cancer, if data from younger patients are used to populate input parameter values to estimate the expected cost and health outcomes of treatment strategies for older patients, analysts and decision-makers will need to appraise whether these sources of evidence are appropriate for the target population of the economic evaluation [12]. Inappropriate input parameter values may result in inaccurate cost-effectiveness estimates, decision uncertainty, and the value of undertaking further research for older patients. Therefore, this study aimed to appraise the sources of evidence and methods to estimate input parameter values in decision-analytic model-based cost-effectiveness analysis of treatments for primary breast cancer in older patients ($\geq$ 70 years old). The results from this study were then used to inform recommendations to improve the estimates of key input parameters in future cost-effectiveness analyses of treatments for older patients with primary breast cancer.

Methods

This study reports a systematic review of published economic evaluations of treatments (including surgery and any adjuvant or non-adjuvant treatments) for older females ($\geq$ 70 years old) with early-stage primary breast cancer following the principles of the Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Systematic Reviews (PRISMA) guidance [13]. This review focused on the methods used by the included economic evaluations to estimate four types of input parameters: (i) health-related quality of life (HRQoL), (ii) the natural history of the disease, (iii) the magnitude of relative treatment effects, and (iv) resource use.

Eligibility criteria

The criteria for inclusion and exclusion in the systematic review were based on the PICO framework [14], i.e., Population (older women aged 70 years or more with early-stage primary breast cancer), Intervention (any treatment, including surgery with or without adjuvant therapy), Comparator (any therapy), Outcome (incremental cost and health outcomes), and Study design (full economic evaluation) (Table 1). A full economic evaluation is defined as "the comparative analysis of alternative courses of action in terms of both their costs and consequences" [15], including cost-effectiveness analyses (CEA), cost-utility analyses (CUA) and cost–benefit analyses (CBA) that used a decision-analytic model. Conference abstracts and manuscripts were written in a

Table 1 Systematic review inclusion and exclusion criteria

Concepts	Inclusion criteria	Exclusion criteria
Population and conditions	Older women aged 70 years or more with (operable, Stage I, Stage II, or early) breast cancer	Only the aged below 70 years Only premenopausal women Only male breast cancer Only metastatic breast cancer Only locally advanced breast cancer Only recurrence of breast cancer Unconfirmed breast cancer Only non-invasive breast cancer Other diseases
Intervention	Surgery with/without adjuvant therapy	Head-to-head comparison Test to determine response after treatment Procedures for diagnosis of breast cancer Preventive strategy Preoperative therapy Nursing or rehabilitation care
Comparison	Any treatments	Treatments or prevention for adverse drug events Treating of cancer complication Follow up strategy
Outcome	Any outcome	Non-economic evaluation outcome, e.g., treatment preference or quality of life
Study Design	Full economic evaluation (CUA, CEA, CUA) that used a decision-analytic model in a peer-reviewed publication	Partial economic studies (cost of illness study, outcome description, cost description, outcome and cost descriptions, cost analysis) Systematic review Clinical trials, observational studies
Language	English	Other languages without English translation
Publication	Full-text article	Conference abstract or proceeding, abstract without full article Letter to editors, editorial, commentary, and news

non-English language were excluded (Additional file 1: Appendix 1).

Information sources and search strategy

Ovid EMBASE® (1974 to 2021 Week 35) and Ovid Medline® (1964 to September 2021) were searched electronically from inception until September 2021. The search strategy (Additional file 1: Appendix 2) comprised disease-specific terms for early-stage primary breast cancer and terms to identify published economic evaluations according to the filters reported by the Centre for Reviews and Dissemination [16].

Study selection and data collection

The titles and abstracts identified by the search strategy were screened independently for relevance against the inclusion criteria by two investigators (YW and LCC). The full texts of eligible studies were further retrieved and reviewed independently by two investigators (YW and LCC) to finalise study selection. At the full-text review stage, the age of the target population for the base-case analysis and, if relevant, for any age-specific subgroup analyses was identified within each economic evaluation to determine whether the study was designed for patients who were at least 70 years old. Discrepancies were resolved through consultation with a third reviewer (SG) to make a final decision.

Data items

Data extraction comprised two stages. In the first stage, the following data were extracted from each economic evaluation by one author (YW): (1) study design (country; target population; strategies compared), (2) study characteristics (evaluation method, i.e., CEA or CUA; type of decision-analytic model; time horizon; perspective; health outcome measure used, and costs included), (3) evidence sources that were used to estimate four types of input parameter values (HRQoL; the natural history of the disease; relative treatment effect; and resource use/cost), (4) methods of analysis (whether deterministic/probabilistic sensitivity analyses or value of information (VOI) analyses were reported), and (5) estimated results (base-case and sensitivity analyses, VOI, and key drivers of relative cost-effectiveness through sensitivity analysis). In the second stage of data extraction, the characteristics of the estimation sample (sample size and mean age) were extracted from the original sources of evidence used

by the included economic evaluations to estimate their input parameter values.

Quality assessment

The completeness of reporting in each economic evaluation was assessed by 17 items in the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [17]. Full adherence to any item was noted as 'Yes', partially adherence was indicated as 'Partial', and non-adherence as 'No'. Two researchers (YW and LCC) independently appraised each identified economic evaluations' quality. Any discrepancies were discussed with a third reviewer (SG) to make a final decision. Quality assessment was summarised visually and reported by a narrative synthesis.

Data synthesis

The extracted data from each economic evaluation were first reported in a table and summarised by a narrative synthesis. This summary described the sample of included economic evaluations according to the type of decision-analytic model used, the proportion of studies that had a target population of patients at least 70 years old in either the base-case or subgroup analysis, the treatment strategies compared, and the main results of each economic evaluation. For each economic evaluation, the sources of evidence used to estimate four types of input parameter were then appraised to determine whether they were obtained from an estimation sample that corresponded with the age of the target population (i.e., ≥ 70 years old). For the remainder of this study, (1) 'HRQoL' refers to the health state utility values, (2) the 'natural history of disease' refers to the probability of health events in the absence of a treatment effect, (3) the 'relative treatment effect' refers to the magnitude of difference between two treatments, and (4) 'resource use' refers to the direct health care resources consumed by patients. In the cases where evidence for input parameter values was based on an estimation sample of patients aged less than 70 years old, the methods of each economic evaluation were then appraised to determine whether any adjustment or calibration was performed to make these estimated values more appropriate for an older population.

Results

The PRISMA diagram (Fig. 1) illustrates the identification, screening and inclusion of studies. The electronic database searches identified 3544 studies, and 67 were read in full. The final sample comprised seven decision-analytic model-based economic evaluations of treatments for primary breast cancer in patients aged 70 years or more [18–24] (Fig. 1).

Characteristics of included studies

All of the included economic evaluations reported both CEA and CUA. The decision-analytic models used by the identified economic evaluations included a cohort Markov model (n = 3) [20, 21, 24] and a patient-level simulation (n = 2) [22, 23]. Two studies did not report the type of decision-analytic model [18, 19]. All the seven economic evaluations used at least three health states within the structure of their decision-analytic model (disease-free; progressed disease; and dead). Different clinical outcomes were used between the economic evaluations to define the health state for progressed disease, including recurrence, local relapse, or metastasis. The structure of the decision-analytic model in four studies [21–24] also included an additional health state for treatment side effects (Table 2, Full data extraction in Additional file 1: Appendix 3).

Three economic evaluations (43%) had a base-case target population that focused exclusively on older patients aged ≥ 70 years [20, 22, 23]. The two studies by Ward et al. [22, 23] had a base-case target population of patients aged 70 years or older with estrogen-positive invasive breast cancer. Sen et al. [20] reported results for 70 years, 75-years, and 85-years old with early-stage breast cancer. Four economic evaluations (57%) reported cost-effectiveness estimates for older patients as part of subgroup analysis by age [18, 19, 21, 24]. The two studies by Naeim et al. reported results for subgroups of patients aged 75-years and 85-years old who had early-stage node-positive [18] and node-negative [19] breast cancer. Desch et al. [24] reported results for a subgroup of patients aged 60-years to 80-years old with a diagnosis of primary breast cancer, and Skedgel et al. [21] reported results for subgroups of patients aged 70 years and ≥ 80-years old.

Three studies [20, 21, 24] compared surgery alone with either adjuvant chemotherapy alone [24], radiotherapy [20], or chemotherapy ± trastuzumab [21]. The results from these three studies indicated that surgery alone was more cost-effective than surgery plus adjuvant treatments for the older population [20, 21, 24] (Table 2). Two studies compared surgery plus adjuvant chemotherapy with adjuvant chemotherapy ± endocrine therapy [18, 19]. Two studies compared surgery plus adjuvant radiotherapy with adjuvant endocrine therapy and their combination [22, 23]. Of these four studies, which compared different adjuvant strategies, the estimated results suggested that less adjuvant treatment, or less harmful adjuvant treatment (i.e., less intensive radiotherapy or less toxic chemotherapy), was more cost-effective for older patients with breast cancer [18, 19, 22, 23]. No published economic evaluation compared surgery with non-surgical treatment as the initial strategy to manage older patients with primary breast cancer (Table 2).

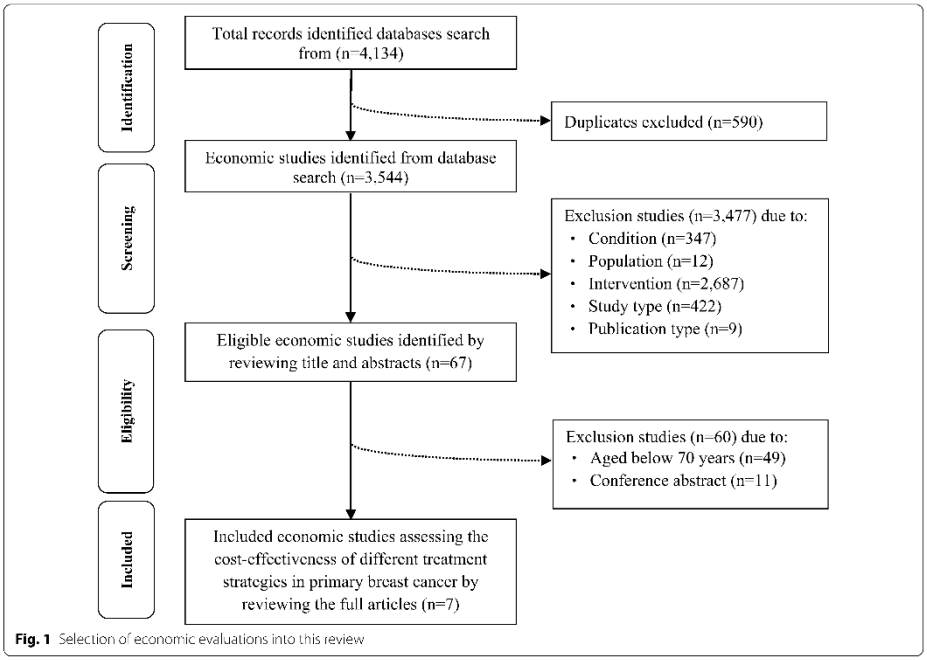

Fig. 1 Selection of economic evaluations into this review

In addition, no identified economic evaluation reported a value of information (VOI) analysis to investigate the need for further research to reduce uncertainty in the estimates of relative cost-effectiveness [25] (Table 2).

Quality assessment

Table 3 reports the quality assessment of the seven economic evaluations according to the CHEERS criteria (Table 3). Thirteen domains of the CHEERS criteria (76%) were reported clearly by the included studies. However, in general, the economic evaluations whose base-case target population comprised older patients exclusively reported the sources of evidence to estimate input parameters more clearly than the economic evaluations that reported results for older patients as part of a subgroup analysis (Table 3). Six economic evaluations partially reported their analytical methods and study parameters which justifies the critical appraisal of these values for the remainder of this review.

Analysis of evidence sources for input parameters

The economic evaluations' sources of evidence and methods to estimate four types of input parameters (HRQoL, natural history, treatment effect, and resource use) are reported below. (Details of Input Parameters in Additional file 1: Appendix 4).

Health-related quality of life

All seven economic evaluations reported expected health outcomes as quality-adjusted life years (QALYs) [18–24]. The EQ-5D instrument was used to estimate HRQoL in four studies [20–23]. Three studies estimated HRQoL values by expert elicitation [18, 19, 24]. Across the included economic evaluations, four approaches were taken to make the HRQoL values a function of the target population's age: (1) HRQoL, which was independent of age; (2) partial age-dependent HRQoL; (3) age-dependent HRQoL with a disutility multiplier; and (4) age-dependent HRQoL with an additive utility decrement (Table 4).

The two studies by Naiem [18, 19] used HRQoL values fixed across age subgroups and independent of the target population's age. Patients were assumed to have lower utility if they received hormone therapy (HRQoL = 0.99), or chemotherapy with minor toxicity (HRQoL = 0.90) or major toxicity (HRQoL = 0.8). Similarly, Desch [24] also assumed that patients had the same utility values after

Table 2 Summary of characteristics for included studies

Study, country	Target population	Type of model	Perspective, type of study	Intervention and Comparator	Results
Surgery plus adjuvant treatments used for comparisons					
Naeim et al. (2005) [18] USA	Subgroup analyses: 45,65, 75, 85 years women with early-stage node (+) breast cancer	Not stated	Health care provider CUA and CEA	Adjuvant chemo alone (CMF) Adjuvant chemo alone (AC) Adjuvant endocrine alone (Tamoxifen) Adjuvant Chemo (CMF) + Tamoxifen Adjuvant Chemo (AC) + Tamoxifen	Adjuvant endocrine treatment was cost-effective in older women
Naeim et al. (2005) [19] USA	Subgroup analyses: 45,65, 75, 85 years women with early-stage node (+) breast cancer	Not stated	Health care provider CUA and CEA	Adjuvant chemo alone (CMF) Adjuvant chemo alone (AC) Adjuvant endocrine alone (Tamoxifen) Adjuvant Chemo (CMF) + Tamoxifen Adjuvant Chemo (AC) + Tamoxifen	Adjuvant endocrine treatment was cost-effective in older women
Ward et al. (2019) [23] USA	Older women targeted: 70 years or older with estrogen-positive invasive breast cancer	Patient level Markov microsimulation	Societal CUA and CEA	Adjuvant radiotherapy (APBI- alone) Adjuvant endocrine (Aromatase inhibitor alone)	Adjuvant endocrine treatment alone was the cost-effective strategy
Ward et al. (2020) [22] USA	Older women targeted: 70 years or older with estrogen-positive invasive breast cancer	Patient level Markov microsimulation	Societal CUA and CEA	Adjuvant endocrine (Aromatase inhibitor alone) Adjuvant radiotherapy (APBI-alone) Their combination	Adjuvant endocrine treatment alone was the cost-effective strategy
Surgery as the comparator strategy					
Desch et al. (1993) [24] USA	Subgroup analyses: 60 to 80 years women with a diagnosis of primary breast cancer	Markov model	Societal CUA and CEA	Surgery alone Adjuvant chemotherapy alone	Adjuvant chemo was not a cost-effective treatment strategy for women aged more than 75 years
Skedgel et al (2013) [21] Canada	Subgroup analyses: 40, 50, 60, 70 and 80 + years women with T1bN0 breast cancer	Markov model	Direct payer CUA and CEA	Surgery alone Adjuvant chemotherapy alone Adjuvant chemotherapy + concurrent trastuzumab Adjuvant chemotherapy + sequential trastuzumab	Concurrent trastuzumab plus adjuvant chemotherapy was a cost-effective strategy
Son et al. (2014) [20] USA	Older women targeted: 70, 75, and 80 years women with early-stage breast cancer	Markov model	Payer CUA and CEA	Surgery alone Adjuvant Radiotherapy EBRT Adjuvant Radiotherapy IMRT	EBRT was the cost-effective strategy

CTx chemotherapy, *RTx* radiotherapy, *ETx* endocrine therapy, *Trz* trastuzumab, *CUA* cost-utility analysis *CEA* cost-effectiveness analysis, *QALY* Quality-adjusted life year, *ICER* Incremental Cost-Effectiveness Ratio, *EBRT* External beam radiation therapy, *IMRT* Intensity-modulated RT, *APBI* accelerated partial-breast irradiation, *AC* adriamycin, cyclophosphamide, *CMF* cyclophosphamide, methotrexate, and 5-fluorouracil

experiencing minor and major side-effects from chemotherapy. This approach may overestimate the expected QALYs accrued by older patients if the loss of HRQoL due to treatment-related adverse events is greater than for younger patients.

Skedgel et al. [21] estimated HRQoL values, which were partially dependent on the age of the target population.

Table 3 Reporting of each economic evaluation according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) criteria

Study	CHEERS criteria																
	Target population and subgroups	Setting and location	Study perspective	Comparators	Time horizon	Discount rate	Choice of health outcomes	Measurement of effectiveness	Measurement and valuation of preference-based outcomes	Estimating resources and costs	Currency, price date, and conversion	Choice of model	Assumptions	Analytical methods	Study parameters	Characterising uncertainty	Characterising heterogeneity
Naeim, et al. (2005) [18]																	
Naeim, et al. (2005) [19]																	
Skedgel, et al. (2013) [21]																	
Sen, et al. (2014) [20]																	
Ward, et al. (2020) [22]																	
Ward, et al. (2019) [23]																	
Desch, et al. (1993) [24]																	

(Note) Key: has the item been reported?

Yes Partial No

The utility values for patients who were 'disease free' were calculated using EQ-5D data from the Medical Expenditure Panel Survey (MEPS) between 2000 and 2002 [26] (n = 38,678 adults). This approach enabled the authors to account for the negative association between age and HRQoL in the general population. However, the HRQoL values for subsequent health states (e.g., recurrence, second recurrence) and adverse events (e.g., nausea) appeared to be fixed and independent of age.

Sen et al. [20] used a disutility multiplier to estimate HRQoL values, which depended on the age of the target population. The MEPS (1998–99) was also used by Sen et al. to estimate age-dependent EQ-5D values for patients after successful treatment to preserve the negative association between age and HRQoL in the general population. Utility values for subsequent health states (e.g., local recurrence) were estimated from a published standard gamble study with 97 patients [27]. The authors then adjusted these utility values using a disutility multiplier based on the mean age-dependent EQ-5D values from the MEPS. This approach ensured that, on average, the HRQoL values accrued by patients who experienced these subsequent health states reflected the observed decline of HRQoL over their lifetimes. For example, the estimated HRQoL value for local recurrence was, therefore, lower for older patients than for younger patients.

Ward et al. [22, 23] used an additive utility decrement to estimate HRQoL values, which depended on the patient's age. A representative cross-sectional survey of the US population (n = 4,000) estimated a baseline EQ-5D value for 70 year old females between 2005 and 2006 [28]. The majority of subsequent health states had a corresponding disutility which was subtracted from this baseline EQ-5D value as an additive decrement (i.e., baseline HRQoL − disutility = new HRQoL). Similar to Sen et al., this approach enabled the authors to estimate HRQoL values for patients who entered subsequent health states, which accounted for the lower HRQoL experienced by older patients, on average, compared with younger patients.

Natural history of the disease

The included economic evaluations used four methods to estimate input parameters that reflected the natural history of breast cancer: (1) data were used from younger patients without adjustment; (2) data were used from older patients without adjustment; (3) plausible values were assumed and varied in a sensitivity analysis, and (4) data were used from younger patients and calibrated for an older population (Table 5).

The two economic evaluations by Naiem et al. [18, 19] estimated the 10-year breast cancer-specific mortality for patients aged 75-years and 85-years old from studies where the estimation sample was younger (e.g., between 50 and 55% of the sample was below 55-years old). This approach may have underestimated the probability of death in the target population if the 10-year breast

Table 4 Sources of evidence to estimate the health-related quality of life

Author, year	Health state	Instrument and data source	Target population	Sample size, mean age	Method of age adjustment
Without adjustment of age					
Naeim et al. (2005) [18] and Naeim et al. (2005) [19]	Disease-free Baseline Progression: hormone therapy minor toxicity with chemotherapy major toxicity with chemotherapy	Not reported Expert elicitation [67, 68]	45 years 65 years 75 years 85 years	150 Not reported	No
Desch et al. (1993) [24]	Disease-free Well Progression: First recurrence Side effect Minor toxicity with chemotherapy Major toxicity with chemotherapy	Not reported Assumptions	60 years 65 years 70 years 75 years 80 years	NA	NA
With adjustment of age					
Skedgel, et al. (2013) [21]	Disease-free: Disease-free baseline varied by age Progression: First local recurrence Second local recurrence Well after relapse Distant recurrence Side effect Congestive heart failure Febrile neutropenia AML/MDS Nausea/vomiting	EQ-5D-3L from previous literature [26] for baseline value Utilities for side effects: from the Cost-Effectiveness Analysis Registry without reporting data source	40 years 50 years 60 years 70 years 80 + years	2981, 74 years [26] Not reported for side effects	Partial adjustment: Age-dependent baseline values and fixed progression state values
Sen et al. (2014) [20]	1. Health states Disease-free: Surgery alone Surgery by different adjuvant treatments Progression: Recurrence Distant metastasis 2. Utility modifier 70–74 y 75–79 y 80–84 y > 85 y	1.EQ-5D from previous literature [27] 2.Standard gamble from previous literature [69]	70, 75, and 80 + years	97 patients with median age at 56 years [27]. Not reported [69]	Disutility multiplier to adjust standard gamble utilities by the mean age-dependent EQ-5D utilities in the general population

Table 4 (continued)

Author, year	Health state	Instrument and data source	Target population	Sample size, mean age	Method of age adjustment
Ward et al. (2020) [22] and Ward et al. (2019) [23]	1. Utility Disease-free Baseline 2. Disutility value: Progression Distant metastasis Second malignancy: radiation Induced salvage mastectomy salvage axillary dissection after axillary recurrence Side effect Fracture Second malignancy: endometrial cancer salvage lumpectomy with radiation treatment of contralateral cancer Cardiac adverse event (MI) DVT Acute radiation dermatitis, Grade 3 Hot flashes Arthralgia Late radiation-induced fibrosis	1. Utility EQ-5D from a cross-sectional U.S. population survey 2005 [28] 2. Disutility from previous economic evaluation [70]	70 years or older	965 patients of a sub-cohort aged 65–74 years [78]	Age-dependent baseline values and health-state utilities with an additive utility decrement

DVT Deep vein thrombosis, *AML/MDS* acute myeloid leukaemia and/or myelodysplastic syndrome, *MI* myocardial infarction

cancer-specific mortality is higher for older patients than younger patients. By contrast, Sen et al. [20] estimated the probability that patients experience health states (e.g., recurrence and metastasis) from published data of a trial that had recruited a sample of older females with breast cancer. It is likely that the probabilities derived from these trial data were more representative of an older population, given that the target population of Sen et al.'s economic evaluation and the estimation sample of the trial had similar patient characteristics.

Skedgel et al. argued that the prior probability of recurrence was unknown for their target population. The authors assumed a range of plausible values for the probability of recurrence across different ages to handle this. One advantage of this approach was that the impact of varying the probability of recurrence on cost-effectiveness estimates could be explored in a sensitivity analysis. Ward et al. [22, 23] estimated transition probabilities using data from a published trial that had whose sample was younger than 70 years old [23, 29–35]. To make these data more representative of an older population, the authors used calibration methods by applying a 'reduction factor' to the annual event rate in both arms of the trial. This approach reduced the absolute risk of events and made the input parameter values more appropriate for an older population.

Magnitude of treatment effects

The economic evaluations used four methods to incorporate age-specific heterogeneity in the relative treatment effects. These methods include (1) direct estimation of age-specific treatment effects from RCT or meta-analysis data; (2) scenario analyses of plausible age-specific treatment effects in the absence of data; (3) the use of observational patient-level data to estimate age-specific treatment effects; and (4) the incorporation of age-specific behavioural parameters to modify the treatment effect.

Skedgel et al. [21] assumed that the relative treatment effect for adjuvant chemotherapy was a function of the patient's age. The authors estimated hazard ratios for 'premenopausal' (40 and 50 years) and 'postmenopausal' (60 and 70 years) patients using RCT data [36, 37]. These data indicated, for example, that adjuvant chemotherapy was less effective at reducing recurrence for older patients (HR: 0.672) than younger patients (HR: 0.563). The authors then assumed that the relative treatment effect for adjuvant trastuzumab was the same for both older and younger patients. Similarly, Desch et al. [24]

Table 5 Sources of evidence to estimate the natural history of the disease

Author, year	Parameters used in studies	Data source	Age of target population	Mean age of estimation sample
From previous economic evaluations				
Skedgel et al. (2013) [21]	Disease-free to recurrence Proportion local recurrence/recurrence 'Instant' conversion from local to distant Side effects Rate of nausea |vomiting (grades 3 + 4) Rate of febrile neutropenia Rate of CHI Relative mortality risk |CHF Rate of AML/MDS Relative mortality rate |AML/MDS Relative risk of cardiotoxicity |conTZ Relative risk of cardiotoxicity |seqTZ	Recurrences from previous economic evaluations [71–73]. Adverse side-effects from previous trials [36, 37]	40 years 50 years 60 years 70 years 80 + years	Patients aged > 70 years account for 16% [36] Patients aged > 60 years account for 16.3% [37]
From randomised controlled trials				
Naeim et al. (2005) [19] and Naeim et al. (2005) [18]	Odds reduction of 10-year mortality Disease-free to death Adjuvant Chemo CMF Adjuvant Chemo AC Adjuvant Tamoxifen Adjuvant Chemo CMF + Tamoxifen Adjuvant Chemo AC + Tamoxifen	Background non-cancer mortality from United States life tables 1997 [74];	45 years 65 years 75 years 85 years	Age-specific mortality from 0 to 100 years
Sen et al. (2014) [20]	Disease-free to recurrence no RT Disease-free to recurrence + RT Recurrence to metastasis Metastasis to death	Clinical trial [29]	70, 75, and 80 years	> 70 years
Ward et al. (2020) [22] and Ward et al. (2019) [23]	Cumulative incidence Disease-free to death Overall survival Death from 2nd cancer Disease-free to progression Ipsilateral breast tumours recurrence Contralateral breast cancer Distant metastasis Side effects Osteopenia requiring bisphosphonate Bone fracture Deep vein thrombosis Fibrosis/soft-tissue necrosis Hot flashes Arthralgia Radiation dermatitis, acute grade 3	Clinical trials [23, 29–35]	70 years or older	70 years [29] > 65 years [30] 65.7 years [31] 57 years [32] Not reported [33]
Desch et al. (1993) [24]	Disease-free to progression First recurrence	Clinical trials [38, 39]	60 years 65 years 70 years 75 years 80 years	48 years [38] Not reported [39]

seqTZ Sequential trastuzumab, *conTZ* concurrent trastuzumab, *AML/MDS* acute myeloid leukaemia and/or myelodysplastic syndrome, *CHF* chemotherapy-related congestive heart failure, *AI* Aromatase inhibitor, *APBI* Accelerated partial-breast irradiation, *AC* adriamycin, cyclophosphamide, *CMF* cyclophosphamide, methotrexate, and 5-fluorouracil

assumed that the annual relative reduction in recurrence for patients aged 60 to 69-years old was 20%, compared with 30% for younger patients, according to data from a meta-analysis of RCTs [38, 39].

Naiem et al. [18, 19] first estimated the relative treatment effect of adjuvant therapies (odds-reduction of 10-year mortality) from a meta-analysis of RCTs for patients aged 45-years and 65-years old [40–43]. In the absence of evidence for the relative treatment effect in 75-years and 85-years old patients, the authors assumed three possible values (low, medium, and high) of treatment effects. In the 'high' scenario, the magnitude of the treatment effect was assumed to be equivalent to that for a 65-year old patient. The authors then estimated how reducing this treatment effect in older patients may impact cost-effectiveness estimates by using the 'medium' and 'low' scenario analyses. The details to calculate the medium values (extrapolated the trend of less benefit with increasing age) and the low values (minimal benefit) were not described explicitly.

Sen et al. [20] incorporated age-specific heterogeneity in the relative treatment effect by performing a patient-level analysis of data from the observational Surveillance, Epidemiology, and End Results (SEER) Program [44]. The authors estimated the 5-year and 10-year overall survival from radiotherapy compared with surgery. The estimated treatment effects were stratified by three age groups (70–74; 75–79; and 80–89 years old).

Ward et al. [22, 23] incorporated a behavioural parameter to reflect evidence that adherence to endocrine therapy may reduce in older patients. Data from a registry study of patients at least 65-years old estimated that compliance with endocrine therapy was 61% at 5-years. In the economic evaluation, this reduction of adherence had a subsequent impact on the relative effectiveness of endocrine therapy. By including this behavioural parameter, the authors were able to model potential changes in the relative effectiveness of treatment as patients became older.

Resources and cost

The included economic evaluations used two methods to estimate input parameters for resource use: (1) estimated input parameters were independent of age, and (2) estimated input parameters were dependent on age (Table 6).

Five economic evaluations assumed that estimates of resource use were independent of each patient's age. Naeim and Keeler [18, 19] estimated the resource use for managing side effects of adjuvant chemotherapy (10% of patients needed treatment to manage low white cell counts, and 3% of patients required hospitalisation for neutropenic fever) based on data from an RCT that had a sample of younger patients (81% of the sample was ≤ 49-years old) [45]. However, this approach may have underestimated the resources required if hospitalisation rates or treatment for low white cell counts are higher in an older population [46]. Skedgel et al. [21] extracted the local and distant recurrence costs from published costing study [47]. These cost estimates were fixed for all age subgroups. The mean age of the sample in the published costing study was not reported, so it was not clear whether these data were applicable for a population of 70 year-old patients with primary breast cancer. Ward [22, 23] estimated direct and indirect costs using a hospital database and clinical guidelines. However, the authors did not report how the estimated cost of the metastatic disease ($23,460) was calculated.

Two economic evaluations estimated age-specific input parameter values for resource use [20, 24]. Desch [24] extracted cost data from the previously published economic evaluations [48, 49] and assumed that total costs of breast cancer treatment decreased as patients got older. This assumption was based on the reduction in follow-up costs, fewer late recurrences, and increased mortality from other causes over time. Sen estimated age-specific (70–74, 75–79, and 80–94 years old at diagnosis) cancer-related costs by conducting a matched cohort study from the SEER-Medicare database. Cancer patients were matched with non-cancer patients based on age, race, comorbidity, region, and year of diagnosis. All costs (inpatient, outpatient, physician, home health, hospice, and Durable Medical Equipment claims) for cancer and non-cancer patients were estimated over the 2-months before and up to 12-months after, date of diagnosis, and then stratified by type of initial treatment received. The cancer-related costs were the difference between the total cost accrued by cancer patients and their matched control [20].

Discussion

Decision-analytic model-based economic evaluations will be essential to help inform the growing interest from decision-makers and clinicians about how best to treat older patients diagnosed with primary breast cancer. However, this review found just seven economic evaluations of treatments for this older population, and all studies compared adjuvant strategies only [18–24]. The authors of these economic evaluations used different methods to estimate input parameters values for HRQoL, the natural history of breast cancer, relative treatment effects, and resource use by using data from both older and younger patient populations. Therefore, a gap exists between the economic evidence required by decision-makers and the economic evidence available currently for managing primary breast cancer in

Table 6 Sources of evidence to estimate resource use

Author, year	Parameters used in studies	Data source	Age of target population	Mean age of estimation sample
Direct cost				
Naeim et al. (2005) [19] and Naeim et al. (2005) [18]	Treatments Adjuvant chemo alone (CMF) Adjuvant chemo alone (AC) Adjuvant endocrine alone (Tamoxifen) Adjuvant Chemo (CMF) + Tamoxifen Adjuvant Chemo (AC) — Tamoxifen	Published guidelines, research studies, and expert opinion of the treatment. Managing side effects of adjuvant chemotherapy from clinical trials [15]	45 years 65 years 75 years 85 years	Not reported
Skedgel et al. (2013) [21]	Treatment TC course FEC-D course 12 months adjuvant trastuzumab, per case Health states Local recurrence, per case Distant recurrence, per case Post-recurrence follow-up, per month Side effect Febrile neutropenia, per case AML/MDS, per month Chemo-related CHF, per month Chemo-related nausea and vomiting, per case Trastuzumab-related cardiotoxicity, per month Palliative trastuzumab, per case	TC course, FEC-D course, febrile neutropenia, AMD/MDS, and chemo related nausea and vomiting from previous literature [72, 73], 12 months adjuvant trastuzumab from previous literature [75], local recurrence, distant recurrence and post-recurrence follow-up from previous literature [47], chemo-related CHF from previous cost-effectiveness analysis [76], and palliative trastuzumab from literature [77]	40 years 50 years 60 years 70 years 80 + years	Not reported
Sen et al. (2014) [20]	Treatments No RT EBRT IMRT Brachytherapy Health states Recurrence, mastectomy Metastatic care Continued phase Death, last year of life	SEER-Medicare Previous costing study [78]	70, 75, and 80 years	70–74 years; 75–79 years; 80–94 years
Desch et al. (1993) [24]	Health states Chemotherapy, if given Side effects Minor toxicity Major toxicity	Previous literature [48, 49] Medical College of Virginia and estimates from Medicare data (1989)	60 years 65 years 70 years 75 years 80 years	Not reported
Direct and indirect cost				
Ward et al. (2020) [22] and Ward et al. (2019) [23]	Treatments Radiation Therapy Anastrozole (per year) Indirect costs of RT Indirect costs of Endocrine Therapy (Annual) Health states Salvage Mastectomy Salvage Lumpectomy or Axillary Dissection Metastatic Disease (per year)	ASCO and National Cancer Centers Network (NCCN) guidelines, all costs were adjusted to 2019 dollars using the US Bureau of Labor Statistics overall Consumer Price Index inflation	70 years or older	Not reported

AC adriamycin, cyclophosphamide, *CMF* cyclophosphamide, methotrexate, and 5-fluorouracil, *HRT* tamoxifen hormone therapy, *AWP* Average Wholesale Prices, *PHS* Public Health Service, *EBRT* external beam radiation therapy, *RT* radiation therapy, *IMRT* intensity-modulated RT

older patients. To help close this evidence gap, the different methods to estimate age-specific input parameters reported in this review can inform the design of future model-based economic evaluations and strategies to overcome the relative scarcity of data from older patients.

A key distinction between the identified economic evaluations was whether they reported cost-effectiveness evidence for older patients as the base-case analysis or as part of subgroup analysis. For example, over half (57%) of economic evaluations in this review reported a subgroup analysis for patients older than 70 years old. Subgroup analyses in economic evaluations are a valuable method to investigate heterogeneity in cost-effectiveness by identifiable patient characteristics [50]. However, it is vital to ensure that input parameter values are appropriate for each subgroup under investigation. If future economic evaluations report age-specific subgroup estimates for older patients with primary breast cancer, decision-makers and analysts should appraise whether the input parameter values are expected to vary across age groups or whether they are independent of age. This will improve the face validity of the model-based analysis and the external validity of the subgroup estimates of cost-effectiveness.

The National Institute for Health and Care Excellence (NICE) Decision Support Unit and the International Society for Pharmaceutical Outcomes Research advise that HRQoL should be estimated using evidence from a population that is similar (e.g., age, sex, and disease severity) to the modelled population [51, 52]. Age is a key determinant of HRQoL because older patients may have lower values than younger patients due to comorbidities and frailty [53]. In this review, the methods used by Ward et al. [22, 23] and Sen et al. [20] to estimate HRQoL (i.e. disutility multipliers or additive utility decrements informed by baseline values from representative surveys of the general population) are helpful techniques for future economic evaluations to incorporate age-specific input parameter values when only data from younger patients are available. Peasgood et al. [54] report a systematic review and meta-regression of health state utility values for breast cancer. Many economic evaluations have previously obtained relevant input parameter values from this study. This meta-regression could be developed further by investigating whether including the mean age of the patients in each study affects the estimated relationship between health state utility and the other variables. Similarly, some studies have used mapping methods to estimate the statistical association between breast cancer-specific patient-reported outcomes (e.g., the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, EORTC QLQ-C30 [55]) and generic instruments used to estimate health state utility values (e.g., EQ-5D) [56–58]. Future mapping studies could build on these earlier studies by including an age variable to account for the impact of older age on HRQoL.

Depending on the decision problem, older patients' natural history of breast cancer may be available to estimate transition probabilities between health states. However, most economic evaluations in this review used evidence from a younger population to estimate these natural history parameters. The calibration method by Ward et al. [22, 23], which adjusted estimates from younger patients so that they were appropriate for an older population, is a helpful technique for future economic evaluations when data from patients over 70 years old are not available. Alternatively, future economic evaluations could use formal expert elicitation methods [59] to estimate these natural history parameters with sensitivity analyses around plausible values. There has also been an increase in the availability of linked primary care, secondary care, mortality, and cancer register data sources [60]. These linked data could also be a valuable source of evidence to estimate the natural history of breast cancer for older patients in routine practice, ensuring that any selection bias and confounding are accounted for.

The magnitude of the estimated relative treatment effects and toxicity for patients with breast cancer can vary by age and type of treatment [61]. For example, chemotherapy and radiotherapy have shown a limited survival benefit for older patients with primary breast cancer than their younger counterparts [61]. Similarly, the effectiveness of endocrine and biological therapy is highly associated with the level and sensitivity of hormone receptors and HER-2 receptors. Older patients have a higher level of ER and PR receptors, whereas a lower level of HER-2 receptors [62, 63]. For future economic evaluations, the target population should be defined clearly in terms of whether a patients' age interacts with the biological mechanisms of disease and, as a consequence, whether the estimated treatment effects are appropriate for that population. The choice of comparator strategies should also be limited to relevant ones for the target population in routine practice. For example, non-surgical strategies may be the most appropriate comparators for patients who are ineligible for surgery due to frailty.

Older patients consume more health care resources than younger patients [63, 64] and costing studies from the US and UK [65, 66] indicated that the main cost drivers for cancer treatment in older populations were from treating side effects and related health care (for example, care and management of chemotherapy-induced neutropenia, radiotherapy-induced skin/gastrointestinal

reaction, and trastuzumab induced cardiotoxicity). It is essential for future economic evaluations of treatments for primary breast cancer to report the evidence sources for resource use transparently to help decision-makers appraise whether these data can generalise to an older population. Sen [20] undertook a matched cohort study to estimate the incremental cost of managing older patients with primary breast cancer. Future research could use a matched cohort design to estimate valuable resource use data for older patients with primary breast cancer using large national observational datasets which link secondary care resource use with cancer diagnosis data. These patient-level data could then provide a better characterisation of how parameter uncertainty in estimates of resource use is distributed.

One limitation of this review was that the search strategy only identified published economic evaluations from peer-reviewed academic journals and may have missed some economic evaluations in the grey literature from government or private organisations. However, the sample of included studies successfully identified a broad range of different methods used to estimate input parameter values for an older population. A second potential limitation was that this systematic review focused only on four specific input parameter types. Therefore, valuable methods to estimate other input parameter types may have been omitted. However, the focus on input parameters for HRQoL, the natural history of the disease, treatment effects, and resource use was sufficient to characterise the majority of essential input parameters for any model-based cost-effectiveness analysis.

Future research could begin to estimate the cost-effectiveness of the different strategies along the full pathway of care observed in routine practice to manage older patients with breast cancer. This economic evidence would be valuable to inform how best to treat these patients by simultaneously considering health outcomes and costs to the healthcare system. Future research could also undertake a value of information analysis, based on the probabilistic outputs from these model-based analyses, to establish whether subsequent primary research in older patients would be worthwhile to reduce uncertainty in estimates of cost-effectiveness. Finally, future research could appraise the sources of evidence and methods to estimate input parameter values within economic evaluations of treatments for older patients diagnosed with other types of primary cancer.

Conclusion

The number of patients older than 70 years of age diagnosed with primary breast cancer is increasing. Health economic evidence will be essential to inform how best to manage these patients. This systematic review found only seven CEAs for this older population, indicating that further economic evidence will be valuable to meet the needs of decision-makers and service commissioners in the future. The methods to estimate input parameters described in this systematic review can help analysts overcome common data challenges to improve the accuracy of expected cost and health outcome estimates. Well-designed observational studies using national register data and formal expert elicitation exercises also present a considerable opportunity to improve the quality of input parameters estimates for this older patient population. A greater emphasis on understanding the cost-effectiveness of care for older patients with primary breast cancer will simultaneously improve population health outcomes, clinical decision-making for these patients, and the allocation of limited resources for health care.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12962-022-00342-7.

Additional file 1: Appendix 1. Reasons for excluding studies. **Appendix 2**. Search Strategy for Databases. **Appendix 3**.Full Data Extraction Tables. **Appendix 4**. Details of Input Parameters.

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Not applicable.

Authors' contributions
All authors contributed to the study conception and design. Study design, data collection and interpretation were performed by YW, SPG, and I-CC. YW wrote the first draft of the manuscript, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
Supplement information is included in the appendices.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
All authors (Yubo Wang, Sean P Gavan, Douglas Steinke, Kwok-Leung Cheung, and I-Chia Chen) declare no conflict of interest.

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Publisher's Note

Appendix 4. Chapter 3: PRIMSA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction, final paragraph
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Method, inclusion, and exclusion
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Method, Literature search
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Method, Literature search
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Method, Study selection
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Method, Data extraction

Section and Topic	Item #	Checklist item	Location where item is reported
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Method, Data extraction
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Method, Data extraction
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Method, Data synthesis
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	Method, Data synthesis
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Method, Data synthesis
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Method, Data synthesis
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Method, Data synthesis
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Method, Data synthesis
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	Method, Data synthesis
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Method, Data synthesis
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Method, Data synthesis
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not report

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Results, selection of studies
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Results, selection of studies
Study characteristics	17	Cite each included study and present its characteristics.	Results, study characteristics
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Results, Quality appraisal of studies measuring HSUV in older women
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimates and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	Results, study characteristics
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Results, Regression analysis
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results, Regression analysis
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not reported
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not reported
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not reported
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion

Section and Topic	Item #	Checklist item	Location where item is reported
	23b	Discuss any limitations of the evidence included in the review.	Discussion
	23c	Discuss any limitations of the review processes used.	Discussion
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Method
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Method
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Method
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	NA
Competing interests	26	Declare any competing interests of review authors.	NA
Availability of data, code, and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Appendices

Appendix 5. Chapter 3: Search strategy for databases

Search strategy for Ovid MEDLINE(R) 1946 to September Week 2 2021

1	Economics/
2	exp "Costs and Cost Analysis"/
3	Economics, Dental/
4	exp Economics, Hospital/
5	Economics, Pharmaceutical/ or Economics, Medical/ or Economics, Nursing/
6	value for money.ti,ab.
7	budget$.ti,ab.
8	(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
9	(expenditure$ not energy).ti,ab.
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	((energy or oxygen) adj cost).ti,ab.
12	(metabolic adj cost).ti,ab.
13	((energy or oxygen) adj expenditure).ti,ab.
14	11 or 12 or 13
15	10 not 14
16	letter.pt.
17	editorial.pt.
18	historical article.pt.
19	16 or 17 or 18
20	15 not 19
21	Animals/
22	Humans/
23	21 not (21 and 22)
24	20 not 23
25	exp Breast Neoplasms/
26	exp Breast/ or exp Breast Diseases/
27	exp Neoplasms/
28	(cancer$ adj3 breast$).tw.
29	(neoplas$ adj3 breast$).tw.
30	(carcinoma$ adj3 breast$).tw.
31	(adenocarcinoma$ adj3 breast$).tw.
32	(tumour$ adj3 breast$).tw.
33	(tumor$ adj3 breast$).tw.
34	(malignan$ adj3 breast$).tw.
35	26 and 27
36	28 or 29 or 30 or 31 or 32 or 33 or 34
37	25 or 35 or 36
38	limit 37 to female
39	Premenopause/
40	38 not 39
41	exp Mastectomy/
42	exp Surgical Oncology/
43	(mastectom$ or operat$ or surg$ or (breast adj conserv$) or lumpectom$ or "wide local excision" or segmentectom$ or mammectom$ or quadrantectom$). ti,ab.
44	41 or 42 or 43

45 24 and 40 and 44

Search strategy for Ovid Embase 1974 to 2021 Week 35

1 health-economics/
2 exp economic-evaluation/
3 exp health-care-cost/
4 exp pharmacoeconomics/
5 1 or 2 or 3 or 4
6 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
7 (expenditure$ not energy).ti,ab.
8 (value adj2 money).ti,ab.
9 budget$.ti,ab.
10 6 or 7 or 8 or 9
11 5 or 10
12 (metabolic adj cost).ti,ab.
13 ((energy or oxygen) adj cost).ti,ab.
14 ((energy or oxygen) adj expenditure).ti,ab.
15 12 or 13 or 14
16 11 not 15
17 animal/
18 exp animal experiment/
19 nonhuman/
20 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh.
21 17 or 18 or 19 or 20
22 16 not 21
23 breast tumor/
24 breast/ or breast disease/
25 neoplasm/
26 24 and 25
27 (cancer$ adj3 breast$).tw.
28 (neoplas$ adj3 breast$).tw.
29 (carcinoma$ adj3 breast$).tw.
30 (adenocarcinoma$ adj3 breast$).tw.
31 (tumour$ adj3 breast$).tw.
32 (tumor$ adj3 breast$).tw.
33 (malignan$ adj3 breast$).tw.
34 27 or 28 or 29 or 30 or 31 or 32 or 33
35 23 or 26 or 34
36 limit 35 to female
37 premenopause/
38 36 not 37
39 radical mastectomy/ or partial mastectomy/ or simple mastectomy/ or modified radical mastectomy/ or subcutaneous mastectomy/ or mastectomy/ or "patient history of mastectomy"/ or extended radical mastectomy/ or prophylactic mastectomy/
40 cancer surgery/ or surgical oncology/
41 (mastectom$ or operat$ or surg$ or (breast adj conserv$) or lumpectom$ or "wide local excision" or segmentectom$ or mammectom$ or quadrantectom$).ti,ab.

42 39 or 40 or 41
43 22 and 38 and 42

Appendix 6. Chapter 3: Full data extraction tables

Table A6.1. Full Data Extraction Table for Naeim and Keerler (2005) [1]

Study Design	Study Characteristics	Data Sources	Analysis	Results
Target population: 65-year-old women to 75-and 85-year-old women with early-stage node (-) breast cancer **Alternatives:** Surgery with five treatment options were considered: (a) Cyclophosphamide, methotrexate, and 5-flurouracil (CMF) × 6 chemotherapy, (b) Adriamycin, cyclophosphamide (AC) × 4 chemotherapy, (c) Tamoxifen hormone therapy (HRT)-5 years, (d) Tamoxifen (HRT)-CMF, (e) Tamoxifen (HRT)-AC. **Country:** USA	**Evaluation method:** CEA **Model type:** Not stated **Time horizon:** 10 years **Perspective:** health care provider **Benefit measure:** QALY **Direct costs included:** initial treatment **Indirect costs included:** Not applicable	**Effectiveness:** benefits of adjuvant therapy: meta-analyses conducted by the EBCTCG [2-5] Transition probability: 1999 mortality data from the National Centre of Health Statistics. Economic data **Health-related quality of life:** previous reviews [6, 7] **Resource use:** Published guidelines, research studies, and expert opinion **Unit costs:** 2001 Average Wholesale Prices **Discount rate:** 3% for costs and health **Currency (Price year):** US dollar (2001)	**Deterministic sensitivity:** Utility, costs, treatment efficacy and discount rate **Probabilistic sensitivity:** No **Value of information:** No	**Base-case:** HRT for a 65-year-old woman with node (+) ER (+) disease is more cost-effective, $10,194/QALY, than CMF or AC chemotherapy. **Probabilistic analysis:** Not applicable. **Value of information:** Not applicable. **Key drivers of relative cost-effectiveness:** Discount rate

Table A6.2 Full Data Extraction Table for Naeim and Keerler (2005) [8]

Study Design	Study Characteristics	Data Sources	Analysis	Results
Target population: 65-year-old women to 75-and 85-year-old women with early-stage node (+) breast cancer **Alternatives:** Surgery with five treatment options were considered: (a) Cyclophosphamide, methotrexate, and 5-flurouracil (CMF) × 6 chemotherapy, (b) Adriamycin, cyclophosphamide (AC) × 4 chemotherapy, (c) Tamoxifen hormone therapy (HRT)-5 years, (d) Tamoxifen (HRT)-CMF, (e) Tamoxifen (HRT)-AC. **Country:** USA	**Evaluation method:** CEA **Model type:** Not stated **Time horizon:** 10 years **Perspective:** health care provider **Benefit measure:** QALY **Direct costs included:** initial treatment **Indirect costs included:** Not applicable	**Effectiveness:** benefits of adjuvant therapy: meta-analyses conducted by the EBCTCG [2-5] Transition probability: 1997 odds reduction of mortality data from the National Centre of Health Statistics. Economic data [9] **Health-related quality of life:** previous reviews [6, 7] **Resource use:** Published guidelines, research studies, and expert opinion **Unit costs:** 2001 Average Wholesale Prices (AWP) **Discount rate:** 3% for costs and health **Currency (Price year):** US dollar (2001)	**Deterministic sensitivity:** Utility, costs, treatment efficacy and discount rate **Probabilistic sensitivity:** No **Value of information:** No	**Base-case:** HRT for a 65-year-old woman with node (+) ER (+) disease is more cost-effective, $6,520/QALY, than CMF or AC chemotherapy. **Probabilistic analysis:** Not applicable. **Value of information:** Not applicable. **Key drivers of relative cost-effectiveness:** Discount rate

Table A6.3 Full Data Extraction Table for Skedgel (2013) [10]

Study Design	Study Characteristics	Data Sources	Analysis	Results
Target population: Women with T1bN0 breast cancer aged 40, 50, 60 and 70 **Alternatives:** Four strategies: (i) no adjuvant chemotherapy or trastuzumab (baseline), (ii) adjuvant chemotherapy alone, (iii) adjuvant chemotherapy plus concurrent trastuzumab and (iv) adjuvant chemotherapy plus sequential trastuzumab. **Country:** Canada	**Evaluation method:** CEA **Model type:** Markov model **Time horizon:** Lifetime **Perspective:** Direct payer **Benefit measure:** QALY **Direct costs included:** HER-2/neu testing, acquisition costs, drug administration, supportive medications and cardiac monitoring **Indirect costs included:** Not applicable	**Effectiveness:** Efficacy: clinical trials [11-13] Recurrences and adverse side-effects: previous literature [11, 13-16] **Health-related quality of life:** Cost-Effectiveness Analysis (CEA) Registry and previous literature [17]. **Resource use:** Previous literature [11-16] **Unit costs:** Statistics Canada consumer price index, health and personal care component **Discount rate:** 3% for costs and health **Currency (Price year):** Canadian dollars (2011)	**Deterministic sensitivity:** Cost, trastuzumab duration of benefit, treatment effect, utility, and discount rate. **Probabilistic sensitivity:** Yes **Value of information:** No	**Base-case:** Strategy iii had a greater than 50% likelihood of meeting a $100 000 per QALY gained threshold at 10-year baseline recurrence rates more than 29%–35% in the ages 40, 50 and 60 cohorts. **Probabilistic analysis:** The minimum recurrence rates necessary to meet a $100 000 threshold were reduced to between 23% and 30% under strategy iii for the age 40, 50 and 60 cohorts and to 35% in the age 40 cohort under strategy iv. **Value of information:** Not applicable. **Key drivers of relative cost-effectiveness:** Chemotherapy without trastuzumab over the entire recurrence range tested

Table A6.4 Full Data Extraction Table for Sen (2014) [18]Sen, Wang [379]

Study Design	Study Characteristics	Data Sources	Analysis	Results
Target population: Older women with early-stage breast cancer aged 70, 75, and 80 years **Alternatives:** Four strategies: (i) No Radiotherapy (ii) External beam radiation therapy (EBRT) (iii) Intensity modulated RT (IMRT) **Country:** USA	**Evaluation method:** CEA **Model type:** Markov model **Time horizon:** Lifetime **Perspective:** Payer **Benefit measure:** QALY **Direct costs included:** Initial treatment, costs to Medicare (inpatient, outpatient facility, physician, home health, hospice, and Durable Medical Equipment claims) **Indirect costs included:** Not applicable	**Effectiveness:** Transition probability: C9343 trial [19]; Overall survival: The Surveillance, Epidemiology, and End Results (SEER)–Medicare database. **Health-related quality of life:** The literature [20-22] **Resource use:** Observational data and literature [23, 24] **Unit costs:** The Surveillance, Epidemiology, and End Results (SEER)–Medicare database **Discount rate:** 3% for costs and health **Currency (Price year):** US dollar (2012)	**Deterministic sensitivity:** One-way sensitivity analysis: the cost of RT, utility of RT, treated-recurrence probability, metastasis probability, and cost of recurrence; Two-way sensitivity analysis: The reduction in recurrence and improvement in age-specific QoL would need to be for the newer modalities to be cost-effective. **Probabilistic sensitivity:** Yes **Value of information:** No	**Base-case:** The ICER for EBRT of $38300 per QALY. The ICER for IMRT were between $70200 per QALY and $79300 per QALY **Probabilistic analysis:** EBRT had a 54.6% probability of cost-effectiveness over no RT at a willingness-to-pay threshold of $100000 per QALY for women aged 70 years **Value of information:** Not applicable. **Key drivers of relative cost-effectiveness:** The utility benefit of RT

Table A6.5 Full Data Extraction Table for Ward (2020) [25]

Study Design	Study Characteristics	Data Sources	Analysis	Results
Target population: Patients age 70 years or older with estrogen positive invasive breast cancer **Alternatives:** Three strategies: (i) an aromatase inhibitor (AI-alone) for 5 years, (ii) a 5-fraction course of accelerated partial-breast irradiation using intensity-modulated radiation therapy (APBI-alone), (iii) their combination. **Country:** USA	**Evaluation method:** CEA **Model type:** Patient-level Markov microsimulation **Time horizon:** Lifetime **Perspective:** Societal **Benefit measure:** QALY **Direct costs included:** Treatment, imaging test and lab test, toxicity, and salvage treatment **Indirect costs included:** Costs for the consult, simulation, treatment visits, and follow-up visit.	**Effectiveness:** Transition probability: clinical trials [26-33] **Health-related quality of life:** Literature [34] **Resource use:** Hospital database and guidelines **Unit costs:** United States Bureau of Labor Statistics Consumer Price Index Inflation Calculator 2020 **Discount rate:** 3% for costs and health **Currency (Price year):** US dollars (2019)	**Deterministic sensitivity:** One-way deterministic sensitivity analysis was performed on each parameter individually **Probabilistic sensitivity:** Yes **Value of information:** No	**Base-case:** The strategy of AI-alone ($12,637) was cheaper than both APBI-alone ($13,799) and combination therapy ($18,012). **Probabilistic analysis:** AI-alone was cost-effective at $100,000/QALY in 50% of trials, APBI-alone in 28% and the combination in 22%. **Value of information:** Not applicable **Key drivers of relative cost-effectiveness:** Not reported

Table A6.6 Full Data Extraction Table for Ward (2019) [31]

Study Design	Study Characteristics	Data Sources	Analysis	Results
Target population: Patient aged 70 years or older with early-stage breast cancer **Alternatives:** Two adjuvant therapy strategies were considered: (iv) AI without radiation therapy (AI-alone, "standard"); (v) Radiation therapy without AI (RT-alone, "experimental"). **Country:** USA	**Evaluation method:** CEA **Model type:** Markov microsimulation model **Time horizon:** Lifetime **Perspective:** Societal **Benefit measure:** QALY **Direct costs included:** Treatment, imaging test and lab test, toxicity, and salvage treatment **Indirect costs included:** Costs for the consult, simulation, treatment visits, and follow-up visit.	**Effectiveness:** Transition probability: clinical trials [26-33] **Health-related quality of life:** Literature [34] **Resource use:** Hospital database and guidelines **Unit costs:** United States Bureau of Labor Statistics Consumer Price Index Inflation Calculator 2019 **Discount rate:** 3% for costs and health **Currency (Price year):** US dollars (2018)	**Deterministic sensitivity:** One-way deterministic sensitivity analysis was performed on each parameter individually **Probabilistic sensitivity:** Yes **Value of information:** No	**Base-case:** The overall ICER of the base case for RT alone compared with AI alone was $210,101 per QALY on average. **Probabilistic analysis:** In 62% of trials, the AI-only strategy was more cost-effective than RT only at the $100,000-per-QALY threshold. A display the acceptability curve, with AI alone as the preferred strategy for all willingness-to-pay levels less than approximately $200,000 per QALY. **Value of information:** Not applicable **Key drivers of relative cost-effectiveness:** Cardiac comorbidities were a more significant driver of mortality than radiation therapy

Table A6.7 Full Data Extraction Table for Desch (1993) [35]

Study Design	Study Characteristics	Data Sources	Analysis	Results
Target population: Postmenopausal women from ages 60 to 80 years with a diagnosis of primary breast cancer **Alternatives:** Adjuvant chemotherapy in elderly women with breast cancer **Country:** USA	**Evaluation method:** CUA and CEA **Model type:** Markov model **Time horizon:** Lifetime **Perspective:** Societal **Benefit measure:** QALY **Direct costs included:** Costs to the health service of chemotherapy, major and minor toxicity **Indirect costs included:** Not considered	**Effectiveness:** Transition probability: Clinical trials [36, 37] **Health-related quality of life:** Literature [38] **Resource use:** Costs and quantities of resources were not separately identified. The costs in the last year of life were an estimate based on two published estimates. **Unit costs:** Charges in 1989 at the Medical College of Virginia and estimates from Medicare data **Discount rate:** 5% for costs and health **Currency (Price year):** US dollars (1990)	**Deterministic sensitivity:** A set of one-way and multi-way sensitivity analyses were performed on the parameters of the model. **Probabilistic sensitivity:** No **Value of information:** No	**Base-case:** The costs per QALY were $28,200 (aged 60), $31,300 (aged 65), $36,300 (aged 70), $44,400 (aged 75) and $57,100 (aged 80) Using active life expectancy, the costs per QALY of adjuvant chemotherapy in elderly women with breast cancer increased to $59,300 (aged 65), $75,000 (aged 70), $96,000 (aged 75) and $212,500 (aged 80). **Probabilistic analysis:** Not applicable **Value of information:** Not applicable **Key drivers of relative cost-effectiveness:** Not reported

Reference A6

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Appendix 7. Chapter 3: Details of input parameters

Table A7.1 Source of evidence to estimate the health-related quality of life

Author (year)	Age of target population	Health state	Utility value	Instrument	Data source	Sample size (n)	Mean age of estimation sample	Method of age adjustment
Naeim and Keeler (2005) a	65-85 years	**Disease free** Baseline **Progression**: Baseline for hormone therapy Baseline for minor toxicity with chemotherapy Baseline for major toxicity with chemotherapy	 1.0 0.99 0.9 0.8	Not reported	Expert elicitation	150	Not reported	No
Naeim and Keeler (2005) b	65-85 years	**Disease free** Baseline **Progression**: Baseline for hormone therapy Baseline for minor toxicity with chemotherapy Baseline for major toxicity with chemotherapy	 1.0 0.99 0.9 0.8	Not reported	Expert elicitation	150	Not reported	No
Skedgel (2013)	40 years 50 years 60 years 70 years	**Disease free**: Disease-free baseline, 70–79 Disease-free baseline, 80+ **Progression**: First local recurrence Second local recurrence Well after relapse Distant recurrence	0.81 0.78 0.70 0.50 0.90 0.60 0.87 0.47	EQ-5D-3L for baseline value	Data derived from previous literature [380] for the baseline utility values	2981	74 years [380]	Partial adjustment: Age-dependent baseline values, and fixed progression state values

Author (year)	Age of target population	Health state	Utility value	Instrument	Data source	Sample size (n)	Mean age of estimation sample	Method of age adjustment
		Side effect Congestive heart failure Febrile neutropenia AML/MDS Nausea/vomiting	0.26 0.85	Not reported for health-related Quality of Life	Health-related Quality of Life was identified from the Cost-Effectiveness Analysis Registry	Not reported	Not reported	
Sen (2014)	70, 75, and 80 years	**Utilities according to treatment and recurrence status:** Conservative surgery and radiation therapy with no recurrence Conservative surgery and radiation therapy with isolated local recurrence Conservative surgery alone with no recurrence Conservative surgery alone with isolated local recurrence Distant metastases **Utility modifier according to age** 70–74 y 75–79 y 80–84 y >85 y	 0.92 0.82 0.88 0.81 0.71 0.716 0.675 0.623 0.59	1. EQ-5D [203] 2. Standard Gambles [381]	1.Recurrence value elicited from previous literature [203] 2.value derived from previous literature	1.97 Not reported 2. Not reported using national censor data source	Not reported [203] The age-specific group reported from 30 to 85 with 5-year interval-group	Age-dependent baseline values, and health-state utilities by multiplying the standard gamble utilities by the mean age-specific utility
Ward (2020)	70 years or older	**Disease free** Baseline **Progression** *Distant Metastasis	 0.84 [205] 0.22 [382, 383]	EQ-5D	Values derived from a cross-sectional U.S. population survey 2005	965 of a sub-cohort for the patients	65-74 years	Age-dependent baseline values, and health-state

Author (year)	Age of target population	Health state	Utility value	Instrument	Data source	Sample size (n)	Mean age of estimation sample	Method of age adjustment
		*Second Malignancy: Radiation Induced *Salvage Mastectomy *Salvage Axillary Dissection After Axillary Recurrence **Side effect** *Fracture *Second malignancy: Endometrial cancer *Salvage Lumpectomy with Radiation *Treatment of Contralateral Cancer *Cardiac Adverse Event (MI) *DVT *Acute Radiation Dermatitis, Grade 3 *Hot Flashes *Arthralgia *Late Radiation-induced Fibrosis	0.18 [384-386] 0.16 [382, 387] 0.16 [388-390] 0.13 [384, 391] 0.12 [392-395] 0.10 [387] 0.08 [387] 0.07 [396, 397] 0.05 [398, 399] 0.02[400] 0.01 0.01 0.01[400]		Disutility values from previous literature	aged 65-74 years		utilities with an additive utility decrement
Ward (2019)Ward, Vicini [401]	70 years or older	**Disease free** Baseline **Progression** *Distant Metastasis *Second Malignancy: Radiation Induced *Salvage Mastectomy *Salvage Axillary Dissection After	0.84 [205] 0.22 [382, 383] 0.18 [384-386] 0.16 [382, 387] 0.16 [388-390]	EQ-5D	Values derived from a cross-sectional U.S. population survey 2005 Disutility values from previous literature	965 of a sub-cohort for the patients aged 65-74 years	65-74 years	Age-dependent baseline values, and health-state utilities with an additive utility decrement

Author (year)	Age of target population	Health state	Utility value	Instrument	Data source	Sample size (n)	Mean age of estimation sample	Method of age adjustment
		Axillary Recurrence **Side effect** *Fracture *Second malignancy: Endometrial cancer *Salvage Lumpectomy with Radiation *Treatment of Contralateral Cancer *Cardiac Adverse Event (MI) *DVT *Acute Radiation Dermatitis, Grade 3 *Hot Flashes *Arthralgia *Late Radiation-induced Fibrosis	 0.13 [384, 391] 0.12 [392-395] 0.10 [387] 0.08 [387] 0.07 [396, 397] 0.05 [398, 399] 0.02[400] 0.01 0.01 0.01[400]					
Desch, Hillner [197]esch (1993)	60 years 65 years 70 years 75 years 80 years	**Disease free** Well **Progression**: First recurrence **Side effect** Minor toxicity with chemotherapy Major toxicity with chemotherapy	 1.0 0.7 0.9 0.8	Not reported	Assumption without justification	NA	NA	NA

(Note) DVT: Deep vein thrombosis; AML/MDS, acute myeloid leukaemia and/or myelodysplastic syndrome; MI: myocardial infarction; * disutility used in the study.

Table A7.2 Chapter 3: Sources of evidence to estimate transition probabilities

Economic Evaluation		Source of Evidence to Estimate Natural History of Disease				
Author (Year)	**Age of Target Population**	**Probability**	**Value**	**Data Source**	**Sample Size (n)**	**Mean Age of Estimation Sample**
Naeim and Keeler (2005) a	65-85 years	* odds reduction of mortality for CMF × 6 * odds reduction of mortality for AC ×4 * odds reduction of mortality for HRT × 5 year * odds reduction of mortality for HRT× 5 year + CMF * odds reduction of mortality for HRT× 5 year +AC	0.02 0.033 0.25 0.25-0.36 0.27-0.38	United States life tables, 1997; benefits of adjuvant therapy: meta-analyses conducted by the EBCTCG	US population	Age-specific mortality from 0 to 100 years
Naeim and Keeler (2005) b	65-85 years	* odds reduction of mortality for CMF × 6 * odds reduction of mortality for AC ×4 * odds reduction of mortality for HRT × 5 year * odds reduction of mortality for HRT× 5 year + CMF * odds reduction of mortality for HRT× 5 year +AC	0.02 0.033 0.25 0.25-0.36 0.27-0.38	United States life tables, 1997; benefits of adjuvant therapy: meta-analyses conducted by the EBCTCG	US population	Age-specific mortality from 0 to 100 years
Skedgel (2013)	40 years 50 years 60 years 70 years	Proportion local recurrence/recurrence 'Instant' conversion from local to distant Rate of nausea|vomiting (grades 3 + 4) Rate of febrile neutropenia Rate of CHF Relative mortality risk|CHF Rate of AML/MDS Relative mortality rate|AML/MDS Relative risk of cardiotoxicity|conTZ Relative risk of cardiotoxicity|seqTZ	25% 20% 2.96% 4.94% 0.02% 2.00 0.39% 2.00 115.68 90.38	Recurrences from clinical trials and meta-analysis; and adverse side-effects from previous literature	1703[402] 1944 Not reported	Patients aged >70 years account for 16% Patients aged >60 years account for 16.3% 50-69 years
Sen (2014)	70, 75, and 80 years	Transition probability: disease-free to recurrence no RT Transition probability: disease-free to recurrence + RT Transition probability: recurrence to metastasis Transition probability: metastasis to death	0.01 12 months 0.18 12 months 0.005 12 months 0.210-0.238 12 months	Clinical trial	636	> 70years

Ward (2020)	70 years or older	# Cumulative incidence for ipsilateral breast tumours recurrence	APBI: 2.1% AI: 3.9% APBI+AI: 1.1%	Clinical trials	636 1326 869	> 70years >65 years 65.7
		# Cumulative incidence for distant metastasis	APBI: 2.1% AI: 1.8% APBI+AI: 1.8%		1135 1009	years[216] 57 years Not reported
		# Cumulative incidence for contralateral breast cancer	APBI: 3.0% AI: 0.8% APBI+AI: 0.8%			
		# Cumulative incidence for overall survival	APBI: 80.2% AI: 80.4% APBI+AI: 80.4%			
		# Cumulative incidence for death from 2nd cancer	APBI: 0.28% AI: 0.08% APBI+AI: 0.11%			
		# Cumulative incidence for Osteopenia requiring bisphosphonate	APBI: 4.7% AI: 16.3% APBI+AI: 16.3%			
		# Cumulative incidence for bone fracture	APBI: 13.0% AI: 15.1% APBI+AI: 15.1%			
		# Cumulative incidence for deep vein thrombosis	APBI: 0% AI: 1.60% APBI+AI: 1.59%			
		# Cumulative incidence for fibrosis/soft-tissue necrosis	APBI: 0.7% AI: 0% APBI+AI: 0.7%			
		# Cumulative incidence for hot flashes	APBI: 16.0% AI: 34.9% APBI+AI: 34.9%			
		# Cumulative incidence for arthralgia	APBI: 0% AI: 6.2% APBI+AI: 6.2% APBI: 0%			

		# Cumulative incidence for radiation dermatitis, acute grade 3	AI: 0% APBI+AI: 0.5%			
Ward (2019)	70 years or older	# Cumulative incidence for ipsilateral breast tumours recurrence # Cumulative incidence for distant metastasis # Cumulative incidence for contralateral breast cancer # Cumulative incidence for overall survival # Cumulative incidence for death from 2nd cancer # Cumulative incidence for Osteopenia requiring bisphosphonate # Cumulative incidence for bone fracture # Cumulative incidence for deep vein thrombosis # Cumulative incidence for fibrosis/soft-tissue necrosis # Cumulative incidence for hot flashes	APBI: 2.1% AI: 3.9% APBI+AI: 1.1% APBI: 2.1% AI: 1.8% APBI+AI: 1.8% APBI: 3.0% AI: 0.8% APBI+AI: 0.8% APBI: 80.2% AI: 80.4% APBI+AI: 80.4% APBI: 0.28% AI: 0.08% APBI+AI: 0.11% APBI: 4.7% AI: 16.3% APBI+AI: 16.3% APBI: 13.0% AI: 15.1% APBI+AI: 15.1% APBI: 0% AI: 1.60% APBI+AI: 1.59% APBI: 0.7% AI: 0% APBI+AI: 0.7% APBI: 16.0% AI: 34.9% APBI+AI: 34.9%	Clinical trials	636 132 869 1135 1009	> 70years >65 years 65.7 years 57 years Not reported

		# Cumulative incidence for arthralgia # Cumulative incidence for radiation dermatitis, acute grade 3	APBI: 0% AI: 6.2% APBI+AI: 6.2% APBI: 0% AI: 0% APBI+AI: 0.5%			
Desch, Hillner [197]esch (1993)Ward, Vicini [401]	60 years 65 years 70 years 75 years 80 years	First recurrence Relative reduction in breast cancer recurrence with chemotherapy	5 20	Clinical trials	679 524 [220]	48 years Not reported [220]

Note: *Odds reduction used from 10-year mortality; # 5 years cumulative incidence

seqTZ, Sequential trastuzumab; conTZ, concurrent trastuzumab; AML/MDS, acute myeloid leukaemia and/or myelodysplastic syndrome; CHF, chemotherapy-related congestive heart failure; AI: Aromatase inhibitor; Accelerated partial-breast irradiation: APBI

Table A7.3 Chapter 3: Sources of evidence to estimate resource use

Economic Evaluation		Source of Evidence to Estimate Resource Use				
Author (year)	**Age of target population**	**Health state**	**Resource estimate**	**Data source**	**Sample size (n)**	**Mean age of estimation sample**
Naeim and Keeler (2005) a	65-85 years	CMF × 6 AC ×4 HRT × 5 years HRT× 5 years + CMF HRT× 5 years +AC	$4568 (AWP) $2833 (PHS) $5965 (AWP) $2318 (PHS) $6320 (AWP) $3350 (PHS) $10,923 (AWP) $6201 (PHS) $12,320 (AWP) $5686 (PHS)	Published guidelines, research studies, and expert opinion	Not reported	Not reported
Naeim and Keeler (2005) b	65-85 years	CMF × 6 AC ×4 HRT × 5 year HRT× 5 year + CMF HRT× 5 year +AC	$4568 (AWP) $2833 (PHS) $5965 (AWP) $2318 (PHS) $6320 (AWP) $3350 (PHS) $10,923 (AWP) $6201 (PHS) $12,320 (AWP) $5686 (PHS)	Published guidelines, research studies, and expert opinion	Not reported	Not reported
Skedgel (2013)	40 years 50 years 60 years 70 years	TC course FEC-D course 12 months adjuvant trastuzumab, per case Local recurrence, per case Distant recurrence, per case Post-recurrence follow-up, per month Febrile neutropenia, per case AML/MDS, per month Chemo-related CHF, per month Chemo-related nausea and vomiting, per case	$4345 $9055 $55,617 $12,522 $38,088 $45 $18,685 $5964 $1715 $22 $669 $31,241	Previous literature	Not reported	Not reported

		Trastuzumab-related cardiotoxicity, per month Palliative trastuzumab, per case				
Sen (2014)	70, 75, and 80 years	No RT EBRT IMRT Brachytherapy Recurrence, mastectomy Metastatic care Continued phase Death, last year of life	$5593 $15396 $23605 $23628 $6250 $37771 $284 (2–4 y); *$212 (after year 4) $44732	SEER-Medicare *Previous literature	Not reported	70-74 years; 75-79 years; 80-94 years
Ward (2020)	70 years or older	Radiation Therapy Anastrozole (per year) Indirect costs of RT Indirect costs of Endocrine Therapy (Annual) Salvage Mastectomy Salvage Lumpectomy or Axillary Dissection Metastatic Disease (per year)	$5,590 $989 $275 $150 $13,378 $2,632 $23,460	ASCO and National Cancer Centers Network (NCCN) guidelines, all costs were adjusted to 2019 dollars using the US Bureau of Labor Statistics overall Consumer Price Index inflation	Not reported	Not reported
Ward (2019)	70 years or older	Radiation Therapy Anastrozole (per year) Indirect costs of RT Indirect costs of Endocrine Therapy (Annual) Salvage Mastectomy Salvage Lumpectomy or Axillary Dissection Metastatic Disease (per year)	$7476 $970 $595 $147 $13116 $2580 $23000	ASCO and National Cancer Centers Network (NCCN) guidelines, all costs were adjusted to 2018 dollars using the US Bureau of Labor Statistics overall Consumer Price Index inflation calculator	Not reported	Not reported

Desch (1993)	60 years 65 years 70 years 75 years 80 years	Chemotherapy, if given Minor toxicity Major toxicity	$6000 $1500 $10000	Previous literature Medical College of Virginia and estimates from Medicare data (1989)	Not reported	Not reported

Note: AC: adriamycin, cyclophosphamide; CMF: cyclophosphamide, methotrexate, and 5-fluorouracil; HRT: tamoxifen hormone therapy; AWP: Average Wholesale Prices; PHS: Public Health Service; EBRT: external beam radiation therapy; RT: radiation therapy; IMRT: intensity-modulated RT

Appendix 8. Chapter 4: Publication version of Chapter 4

This appendix reported the published version of the systematic review to summarise the health state utility values in postmenopausal women with early-stage breast cancer, and to quantify the association of utility values with age increase to inform the economic evaluation. The systematic review was published in *Health and Quality of Life Outcomes* in December 2022.

The appropriate citation for the study is:

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Health and Quality of Life Outcomes

REVIEW Open Access

The impact of age on health utility values for older women with early-stage breast cancer: a systematic review and meta-regression

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Abstract

Introduction: An increasing number of postmenopausal women are diagnosed with breast cancer at an older age (≥ 70 years). There is a lack of synthesised health utility data to support decision-making for managing breast cancer in this older population. This study aimed to identify the availability of, and the subsequent impact of age on, health state utility values (HSUVs) measured by the EQ-5D for older women with early-stage breast cancer.

Method: This systematic review identified EQ-5D (3L or 5L version) HSUVs for postmenopausal women with early-stage breast cancer. Studies were identified from a previous systematic review (inception to 2009) and an electronic database search (Medline and Embase; 2009 to September 2021). Mean HSUVs were summarised by health state. Quality appraisal was performed on studies reporting HSUVs for older ages (≥ 70 years). Multivariable meta-regression assessed the association between HSUVs and age, health state, treatments received, and time of measuring the utility values (greater or less than one year post-treatment).

Results: Fifty EQ-5D HSUVs were identified from 13 studies. Mean HSUVs decreased as health state worsened: from the stable (mean=0.83) to progression (mean=0.79) and advanced (mean=0.68) states. Two studies reported six HSUVs estimated from the sample of women with a mean age ≥ 70. Meta-regression model fit improved by including age as an independent variable and attenuated the estimated utility decrements associated with worse health states. Utility decrements for the progression and advanced states were -0.052 (95%CI: -0.097, -0.007) and -0.143 (95%CI: -0.264, -0.022) respectively. The breast cancer-specific utility decrement associated with a one-year increase in age was -0.001 (95%CI: -0.004, 0.002).

Conclusion: Relevant and accurate HSUVs are essential to help support decision-making about the most effective and cost-effective ways to manage early-stage breast cancer in older women. Age has a vital role in determining health utility values in this population. This study provides analysts and decision-makers with HSUVs and utility decrements that reflect the disease process in this older population.

Keywords: Early-stage breast cancer, Economic evaluation, Health state utility values, Meta-regression, Older women, Systematic review

Introduction

Health state utility values (HSUVs) quantify preference for specific health states and are a vital source of evidence for health economic evaluations to inform resource allocation decisions and treatment recommendations [1]. Best practice guidance explains how the most relevant HSUVs to inform decision-making should reflect the

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health characteristics of the target patient population [2, 3]. To improve the accuracy of HSUVs for specific populations, there is a growing focus on investigating how the impact of age is quantified across different health conditions [4]. The incidence of health conditions, such as breast cancer, is starting to increase in older patients due to an ageing population [5]. In light of this trend, there is a need to improve the robustness of HSUV estimates and strengthen the evidence base that will support treatment recommendations in these older patient populations.

The quality of life of women with breast cancer varies with different factors. The HSUVs used in economic modelling must reflect the target population's relevant disease health states, treatments received, and patient characteristics [6]. Age is a crucial risk factor influencing the incidence and treatment of female breast cancer [7]. One-third of new breast cancer cases in England were diagnosed at an older age (>70 years) [8]. Older age typically corresponds with lower HSUVs due to weaker physical functioning and multimorbidity [9, 10]. However, there are few health economic evaluations for older women with breast cancer that used HSUVs measured directly from patients aged 70 years or more.

In 2022, a systematic review identified seven economic evaluations of breast cancer treatments for older women [11]. Most studies in this review ($n=6$; 86%) sourced health utility data from patients younger than 70 years, and adjusted these estimates to correspond with an older population. A better understanding of the health utility values available in this growing patient population will be valuable to support the need for economic evidence designed to inform the management of older women with early-stage breast cancer.

A systematic review and meta-regression by Peasgood et al. (2010) [12] synthesised health utility values for early-stage and metastatic breast cancer. Similarly, Kaur et al. (2022) [13] report a meta-regression of health utility values across different stages of breast cancer and treatment. Both studies demonstrate the value of meta-regression to establish whether patient-level and treatment-related variables are associated with mean HSUVs. Although these analyses included several variables associated with health utility (for example, disease health state, treatment, and HSUV valuation method), age was not included as an independent variable in either meta-regression. This specification may overestimate the health utility decrement associated with disease progression. To improve the usefulness of these estimates for generating future economic evidence, including age as an independent variable within a meta-regression will help to estimate its impact on HSUVs for older women with breast cancer.

This study aimed to identify the availability of, and the subsequent impact of age on, HSUVs measured by EQ-5D for older women with early-stage breast cancer. To achieve this aim, there were three objectives: (1) identify studies that estimated HSUVs by EQ-5D in a sample of postmenopausal women with early-stage breast cancer; (2) describe and appraise the quality of HSUV estimates in the subgroup of studies that focussed on older women (aged ≥ 70 years); and (3) evaluate how age affects the statistical association between HSUVs and other relevant variables.

Method

A systematic review to identify all published studies reporting HSUVs for postmenopausal women with early-stage breast cancer was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA 2020) [14] (Supplementary Appendix 1). The protocol for this systematic review is registered at PROSPERO (no. CRD42021232743). After registration, a minor revision was made to only include studies that measured HSUVs by an EQ-5D instrument only, to avoid duplication with another systematic review by Kaur et al. published in 2022 [13]. EQ-5D is the generic multi-attribute measure of health status used most often by health technology assessment bodies around the world. Hence, focusing on the EQ-5D instrument ensures that this study is valuable for health care decision-makers [15].

Inclusion and exclusion criteria

Studies were included if they (i) reported an original HSUV for a specific health state for postmenopausal women with breast cancer e.g., stable (defined as cancer that does not worsen after treatment, or diagnosed as stage I or II), progressed (tumour locally spread or diagnosed as stage III), or advanced disease states (tumour distant metastases or diagnosed as stage IV), (ii) measured using an EQ-5D instrument (EQ-5D-3L or EQ-5D-5L) and valued with a tariff that is used routinely for decision-making, and (iii) were written in English (Table 1). Postmenopausal women as the target population were initially identified by whether the study self-reported the term "postmenopausal women" or not. If not, the cut-off age ≥ 45 years was used to define postmenopause, according to the National Health Service (NHS) in England [16].

Literature search

Relevant studies that met the inclusion criteria were identified in two stages. In the first stage, studies published from inception to 2009 were identified from the systematic review by Peasgood et al. (2010) [12]. The

review by Peasgood et al. (2010) [12] comprehensively searched thirteen databases to identify HSUVs for breast cancer measured using preference-based instruments, and also using Google Scholar as a supplementary data source to identify the target literature. The search strategies in the review by Peasgood et al. (2010) [12] were developed from a previously published systematic review by Hind et al. (2010) [18] for early breast cancer. These two reviews have informed the evidence base for earlier National Institute for Health and Care Excellence (NICE) clinical guidelines and are highly cited in other published reviews or original studies [19–24]. Therefore, the review by Peasgood et al. (2010) was considered to be a good data source for identifying the studies reporting HSUVs in breast cancer before 2009. From this initial set of references, studies that reported HSUVs measured using an EQ-5D instrument were identified and retrieved for full text review.

In the second stage, studies published from 2009 until 21 September 2021 were identified from electronic medical databases by applying structured search strategies to Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions ® 2009 January to 2021 22 September and Ovid EMBASE® from 2009 January to 2021 22 September. The search strategies (Supplementary Appendix 2) included relevant terms for breast cancer used by Peasgood et al. (2010) [12] and HSUVs. Terms to identify HSUVs were sourced from the electronic database search filters reported by the Centre for Reviews and Dissemination [25].

Study selection

The titles and abstracts of studies identified from the electronic database search were screened independently by three investigators (SB, MA, YW) against the inclusion criteria. The concordance between reviewers was calculated by three pairwise intra-class correlation coefficients (ICC) [26]. ICC values less than 0.50, between 0.50 and 0.75, 0.75 and 0.90, and greater than 0.90 indicate poor, moderate, good and excellent reliability, respectively [27]. Three investigators (SB, MA, YW) independently reviewed the full text of eligible studies. Discrepancies were resolved through consensus with other reviewers (SG & LCC) to finalise the selection of studies. This was done to ensure that the reviewers appropriately applied the inclusion and exclusion criteria in the screening process.

Data extraction

Data were extracted from the included studies independently by three reviewers (SB, MA, YW) using a pre-designed data collection form and then merged by YW for analysis. Extracted data included three sections: (1) characteristics of the study, i.e., the author, year and country of the study; (2) methods of health utility valuation, i.e., mean age of estimation sample, instrument to measure health utility values (EQ-5D-3L or EQ-5D-5L), the valuation tariff, and the sample size of the study; and (3) estimated health utility values for specific health states (stable, progression and advanced state), i.e., mean utility value, standard deviation (SD), standard error (SE), interquartile range (IQR), or 95% confidence interval (95%CI). Studies that estimated utility values with the EQ-5D-5L tariff for England [28] were excluded because the National Institute for Health

Table 1 Inclusion and exclusion criteria for the study

Component	Inclusion criteria	Exclusion criteria
Population and conditions	Postmenopausal women with (operable, Stage I, Stage II, or early stage) breast cancer	• Only premenopausal women • Only male breast cancer • Only metastatic breast cancer • Unconfirmed breast cancer • Other diseases
Intervention & Comparator	Any intervention for breast cancer	No restriction on the intervention
Outcome	Study reported at least one original utility value measured by EQ-5D (3L or 5L)	• No original utility value reported • Unspecified/not clearly specified health states relating to breast cancer • Psychometric validation studies • Description of health states without interval properties rather than the valuation of health states • EQ-5D-5L England tariff
Language	English	Other languages without English translation
Publication	Full-text article	Conference abstract or proceeding, abstract without full article, letter to editors, editorial, commentary, and news

The criteria for inclusion and exclusion were based on the PICO framework [17]

and Care Excellence (NICE) does not recommend using the tariff due to concern about data collection and analysis methods [29]. In such circumstances, studies that estimated UK EQ-5D-3L utility values from EQ-5D-5L profiles by a recommended mapping method were included [30].

Data synthesis

Descriptive statistics were first used to present the included studies, study characteristics and the mean (SD or SE), median (IQR) and the range (or 95%CI) of the HSUVs. These results were summarised narratively, presented graphically, and stratified by different health states and treatments where possible for the full sample of postmenopausal women. For studies that did not report the SD, the estimated SD was calculated from the mean value, sample size, SE or 95%CI if necessary, based on the method suggested by the Cochrane Library [31].

The subgroup of studies which estimated HSUVs using a sample of older women (mean age $\geq$ 70 years) were described by the study design, country, mean age of respondent, elicitation method and quality appraisal. As there are no agreed criteria to appraise the quality of HSUVs [26], four questions (in Table 3) were used to appraise the quality of the studies that estimated HSUVs from an older population. These four questions were identified from an appraisal tool (including 17 questions) developed by Nerich et al. (2017) [32] (Full appraisal tool in Appendix 3). According to a systematic review of HSUV appraisal tools by Zoratti et al. [33], these four questions from the tool developed by Nerich et al. (2017) [32] were useful to appraise the quality of breast cancer HSUVs. YW independently appraised the quality of studies, and the results of the appraisal were categorised as yes (complete), yes (partial), no, and not assessable. Publication bias for HSUVs is difficult to determine because they are usually reported as secondary outcomes. Thus, publication bias in this review was not assessed.

The HSUVs were synthesised by a meta-regression following the methods used by Peasgood et al. (2010) [12] to identify the association between HSUVs and different independent variables. A linear regression model was used with the mean HSUV from each study as the dependent variable. Age is a critical factor that influences HSUVs. Therefore, this study compared the results from two regression specifications. The first specification included the reported mean age of the estimation sample for each HSUV as a continuous independent variable. The second specification omitted the reported mean age from the set of independent variables. The performance of these two specifications was compared using the coefficient of determination (R^2) to assess the goodness of fit [34].

According to Peasgood et al.'s review [12], several additional variables that may influence the HSUV measurement and valuation were included in the analysis: disease health state, the instrument to measure health utility, treatment received, and valuation time. Disease health state (stable, progressed disease, or advanced disease states), instrument to measure health utility (EQ-5D-3L or EQ-5D-5L), treatment received (surgery, surgery alone with adjuvant therapies, or unspecified treatment), and valuation time (less or more than one year after diagnosis) were measured as categorical variables. 'Surgery' comprised different types of surgical intervention (for example, mastectomy or breast conserving surgery) to reduce the number of independent variables in the meta-regression, following the approach by Kaur et al. [13].

Other study characteristics (e.g., country of the study, valuation tariff, trial or observational study design, intervention and comparators in the study) were not included as independent variables in the meta-regression. Given the sample size of the meta-regression, this decision was made to prevent collinearity between categorical independent variables. The regression model weighted by the inverse of the SD for each HSUV. This approach gives greater weight to HSUVs values with a smaller SD because they offer better precision in the true utility value than those with a larger SD. Cluster-robust standard errors were used to account for within-study correlation because some studies contributed more than one HSUV to the meta-regression which were likely to be correlated with each other [35]. The meta-regression was performed using Stata 14.0 (Stata Corp, College Station, TX) [36].

Results

Selection of studies

Forty-nine potentially eligible articles were identified from the systematic review by Peasgood et al. [12], and 3,022 articles were identified from the electronic medical database search (Fig. 1). Thirteen studies met the inclusion criteria and were included in the systematic review. The reasons for exclusion are summarised in Fig. 1 and the supplement file (Supplementary Appendix 4). The ICC value indicated good and excellent reliability between reviewers (pairwise ICCs between three reviewers were: 0.78, 0.89 and 0.96).

Study characteristics

Fifty HSUVs were identified from the 13 studies [37–49] (Table 2). The HSUVs were distributed across three health states: stable ($n=33$), progressed disease ($n=10$), and advanced disease ($n=7$). The EQ-5D-3L ($n=43$) [37–46, 48] instrument was used more often than the

EQ-5D-5L instrument ($n=7$) [47, 49]. Six different valuation tariffs were applied across the sample, including the UK 3L ($n=28$) [37–39, 41, 42, 46, 48], US 3L ($n=2$) [40], Canada 3L ($n=4$) [45], Korea 3L ($n=5$) [44], China 3L ($n=4$) [43], China 5L ($n=4$) [47], and Indonesian 5L ($n=3$) [49] tariffs (Fig. 2). Across the whole sample, these HSUV values were estimated from patients with a mean age between 44 and 75 years. One study defined their sample as 'postmenopausal women [49], and the remaining studies (92%) had a sample of women whose mean age was over 45 years.

The subset of health utility values for the stable state ($n=33$, same mean and median: 0.83; range: 0.67 to 0.92) were higher than the progressed disease state ($n=10$, mean: 0.79; median: 0.77; range: 0.72–0.94) and advanced disease state ($n=7$, mean: 0.68; median: 0.69; range: 0.55–0.85) (Fig. 3). Figure 4 (a box-and-whisker plot) reports the distribution of HSUVs by disease state and treatment received. Of the 33 utility values for the stable health state, treatment was not specified for six utility values (mean: 0.78; median: 0.79; range: 0.67-0.89). Patients who received surgery with adjuvant radiotherapy had the highest utility value ($n=3$; mean: 0.86; median: 0.89; range: 0.78–0.90), followed by surgery with adjuvant chemotherapy ($n=19$; mean: 0.85, median: 0.84; range: 0.76-0.92) and surgery alone ($n=1$) or with unspecific adjuvant treatment ($n=3$; same mean and median: 0.80; range: 0.71–0.87).

It was impossible to stratify HSUVs by treatment for progressed and advanced health states, as only one HSUV specified treatment with surgery alone in both the progressed state (0.77) and advanced disease state (0.58). The remaining values for these two health states were not attached to a specific treatment. The mean of these remaining HSUVs was 0.79 for the progressed state ($n=9$; median: 0.78; range: 0.72–0.94), and 0.69 for the advanced state ($n=6$; median: 0.69; range: 0.55–0.85) (Fig. 4). (Detailed mean utility values extracted in each study reported in Appendix 5).

Quality appraisal of studies measuring HSUV in older women

There were 6 HSUVs for the stable disease state estimated specifically from a sample of older patients (mean age ≥ 70 years) in two clinical trials by Williams et al. (2011) [41] ($n=2$) and Sattar et al. (2019) [45] ($n=4$). These two studies are now described in further detail. The quality appraisal criteria are reported in Table 3.

Williams et al. (2011) [41] conducted a clinical trial in the UK with 248 older participants (mean age:

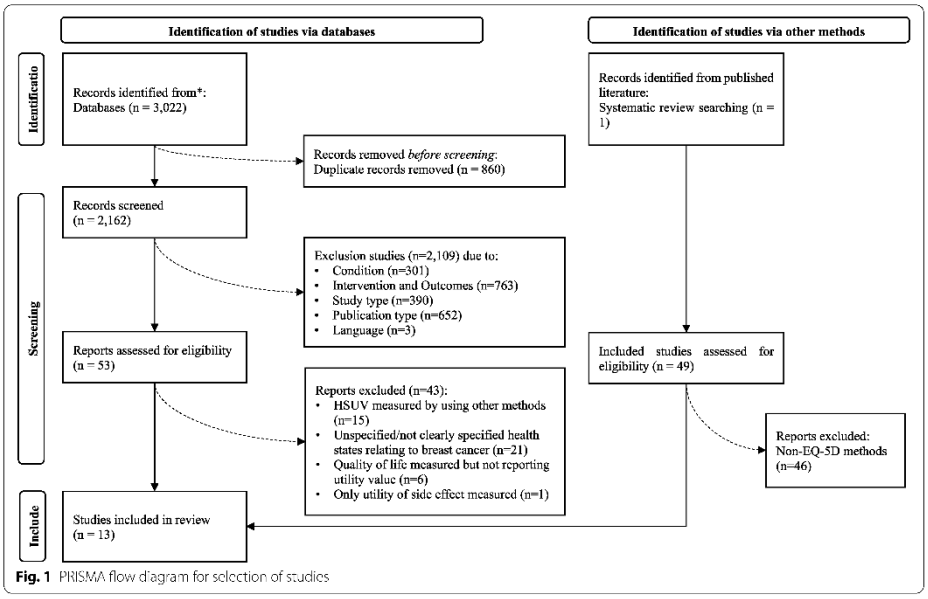


Fig. 1 PRISMA flow diagram for selection of studies

Table 2 Characteristics of identified studies ($n = 13$)

Author	Country	Study period	Study type	Respondent	Method of valuation	Valuation Tariff	Mean Age	Sample size
EQ-5D-3L								
Conner-Spady, et al. (2005) [37]	Canada	04/1995–10/1998	Questionnaire	Patients' own health	EQ-5D-3L	UK	44.7	52
Lidgren, et al. (2007) [38]	Sweden	04–05/2005	Questionnaire	Patients' own health	EQ-5D-3L	UK	57	345
Kimman, et al. (2009) [39]	Netherland	07/2005–09/2007	Questionnaire	Patients' own health	EQ-5D-3L	UK	55.8	192
Freedman, et al. (2010) [40]*	USA	2010	Questionnaire	Patients' own health	EQ-5D-3L	US	45–64	1050
Williams, et al. (2011) [41]	UK	1997	Questionnaire	Patients' own health	EQ-5D-3L	UK	72.8	255
Yousefi, et al. (2016) [42]	Iran	11/2013–06/2014	Questionnaire	Patients' own health	EQ-5D-3L	UK	46.7	163
Wang, et al. (2018) [43]	China	12/2016–03/2017	Questionnaire	Patients' own health	EQ-5D-3L	China	49.1	2828
Yu, et al. (2018) [44]	Korea	01/2012–06/2012	Questionnaire	Patients' own health	EQ-5D-3L	Korea	48.9	226
Sattar, et al. (2019) [45]	Canada	10/2014–10/2015	Questionnaire	Patients' own health	EQ-5D-3L	Canada	75.3	58
Tanaka, et al. (2019) [46]**	Japan	Not stated	Questionnaire	Patients' own health	EQ-5D-3L	UK	53.4/57.6	38
Zigman, et al. (2020) [48]	Croatia	01/2016–12/2016	Questionnaire	Patients' own health	EQ-5D-3L	UK	44.7	114
EQ-5D-5L								
Yang, et al. (2020) [47]	China	08/2017–05/20	Questionnaire	Patients' own health	EQ-5D-5L	China	51.37	446
Etikasari, et al. (2021) [49]	Indonesia	01/2019–08/2019	Questionnaire	Patients' own health	EQ-5D-5L	Indonesian	59.2	126

* Respondent age in Freedman [40] was 45–64 years (57%);

** Respondent age in Tanaka [46] for usual care: 53.4 years, pharmacist care: 57.6 years

72 years, SD: 5) who had primary breast cancer and received surgery or adjuvant endocrine therapy with or without radiotherapy. The duration of follow-up was five years. The EQ-5D-3L instrument and UK tariff [50] was used to estimate the HSUVs. Across both arms, 12 HSUVs in total were estimated at baseline, and 3.5, 9, 15, 36, and 60 months after surgery. The specific health state associated with these HSUVs was not reported. Assuming that patients were stable within 6 months after surgery, at 3.5 months, the HSUVs for adjuvant endocrine therapy alone was 0.77 (95%CI: 0.74 to 0.80), and for adjuvant endocrine therapy plus radiotherapy was 0.78 (95%CI: 0.75 to 0.81).

Sattar et al. (2019) [45] conducted a clinical trial in older participants with breast cancer who received surgery and adjuvant chemotherapy with ($n = 30$, mean age: 75 years) and without (the usual care; $n = 28$, mean age: 75 years) a geriatric assessment in Canada. The EQ-5D-3L instrument and Canadian tariff [51] was used to estimate the HSUVs. Across both arms, eight HSUVs were estimated at baseline and 3, 6, and 12 months. The specific health state associated with these HSUVs was not reported. Assuming that patients were stable within 6 months after surgery, the median HSUVs for patients with the geriatric assessment at 3 and 6 months were 0.82 (IQR: 0.29), and 0.82 (IQR: 0.27), respectively. The median HSUVs for patients without the geriatric assessment at the same time periods were 0.78 (IQR: 0.15), and 0.83 (IQR: 0.22).

Both two studies completed or partially reported four questions of the quality appraisal tool (Table 3). Williams et al. (2011) [41] reported the reason for selecting the EQ-5D-3L instrument to measure the HSUVs was due to the recommendations by the NICE reference case, and fully explained the reason to use the EQ-5D-3L UK valuation tariff. Both studies [41, 45] fully reported details about characteristics of study population as they are randomised control trials. Therefore, the two studies [41, 45] are high quality studies based on this quality appraisal tool.

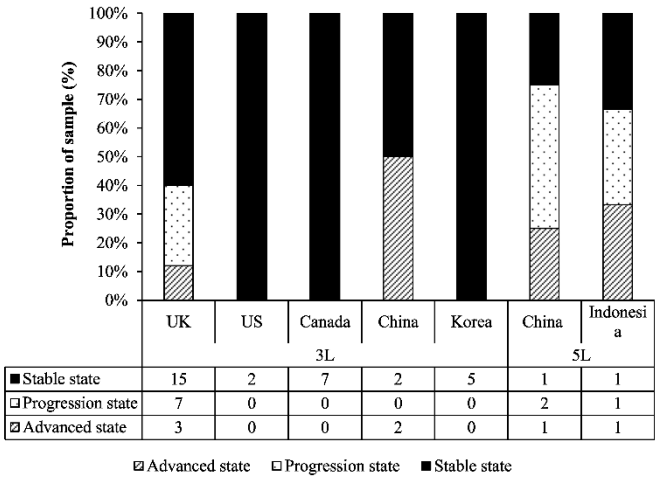


Fig. 2 Health state utility values by health state and valuation tariff

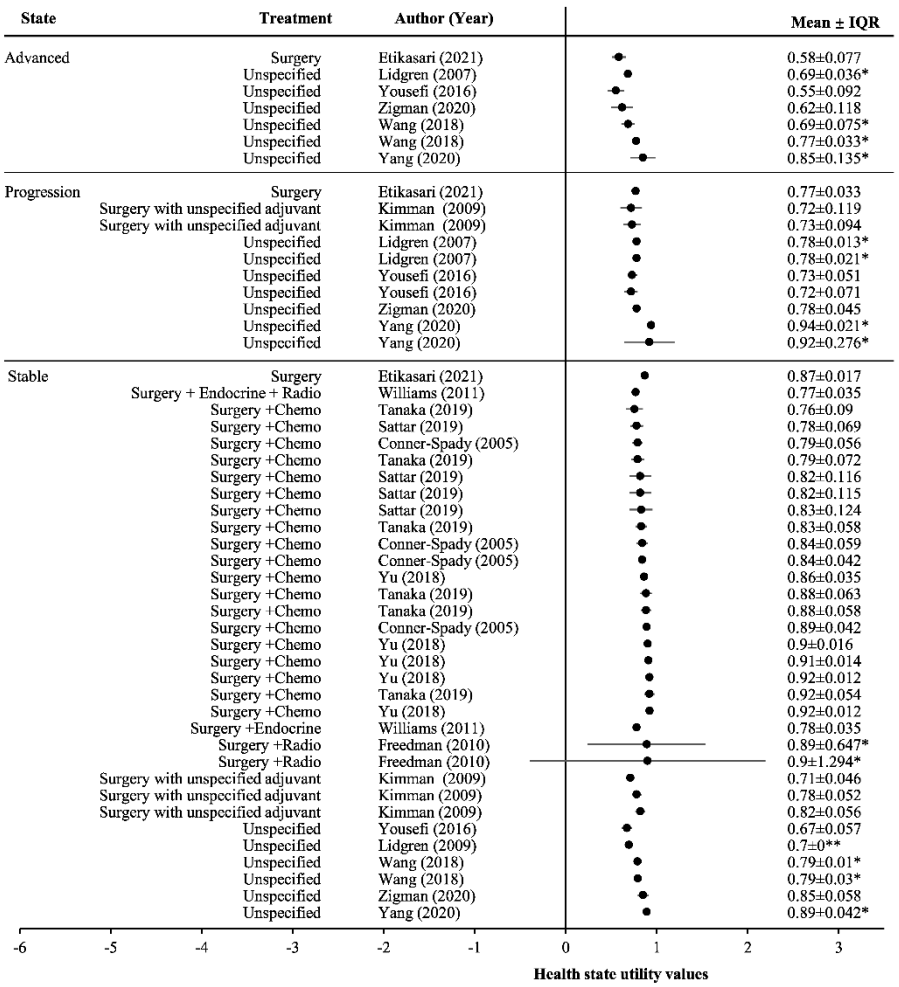
Regression analysis

Table 4 reports the results of the meta-regression analyses. The specification that included age as an independent variable had a better goodness of fit (R^2 increased from 0.686 to 0.691). Across all model specifications, the variables for disease health state, treatment, and instrument to measure HSUVs had a statistically significant ($p < 0.05$) association with the mean HSUV. Age was estimated to have a negative but non-statistically significant coefficient (-0.001, 95%CI: -0.004 to 0.002). This result indicates that expected HSUVs reduce as postmenopausal women with breast cancer become older. The statistically significant and negative coefficients on progression (-0.052) and advanced disease states (-0.143) indicated that expected HSUVs reduce as disease worsens. Compared with surgery alone, adjuvant treatments improved the mean HSUVs with an increment of 0.205 for adjuvant chemotherapy, 0.200 for adjuvant radiotherapy, and 0.085 for adjuvant endocrine therapy. The HSUV for patients over one year after treatment was 0.045 units higher than those who received treatment within one year.

Discussion

This study provides a valuable set of utility values for older women with early-stage breast cancer to support future economic analyses and decision-making. Six utility values for patients with stable breast cancer, measured HSUVs from an older population with mean age ≥ 70 years, were identified from two studies conducted in the UK [41] and Canada [45]. In addition, the meta-regression quantified the disease-specific age-related utility decrement for older women with breast cancer and provided improved estimates of HSUV modifiers for age by controlling for disease state and treatment. Collectively, these estimates improve the robustness of evidence for future quality of life research and health economic evaluations for older women with breast cancer.

There is consensus among healthcare providers that the quality of life for women with breast cancer reduces with ageing due to comorbidity and frailty related to poor physical functioning [52]. Therefore, it is necessary to incorporate this reduction of health utility within economic evaluations to improve the robustness of quality-adjusted life year (QALY) estimates [2]. The association of HUSVs with other key factors, including treatment types (e.g., mastectomy or non-specified surgery type, adjuvant chemotherapy or radiotherapy), valuation methods (e.g., EQ-5D, standard gamble, time trade-off), and valuation respondents (patients, clinicians or scenario), has been assessed by previously published studies (Peasgood et al. (2010) [12] and Kaur et al. (2022) [13]). Our study quantified the association between HSUVs and age by controlling for similar variables. The results of the meta-regression in our review provide insights for health care analysts undertaking future

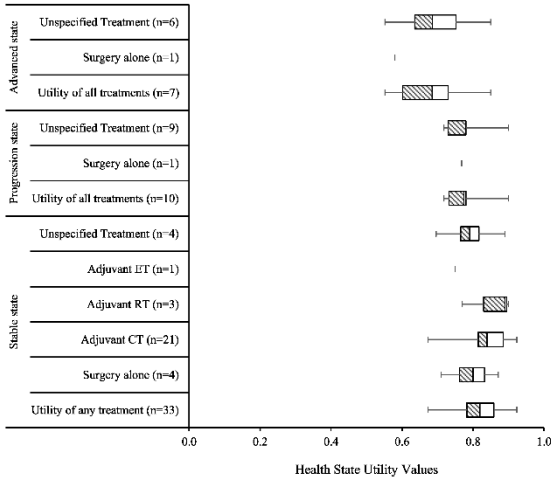


(Note) IQR: interquartile range; *: standard deviation estimated; **: no standard deviation reported or standard deviation cannot be estimated. Chemo: chemotherapy; Radio: radiotherapy; Unspecified: treatment unspecified

Fig. 3 Health state utility values by health state

research to improve decision-making for breast cancer management in older women.

For healthcare decision-makers who use health economic evidence, decisions are made according to the incremental expected cost and health benefits of care irrespective of whether differences are statistically significant [53]. Therefore, although the association between age and HSUVs had no statistical difference in



(Note) In the box and whisker plot, the bottom and top of the box are the 25th and 75th percentile. The middle band of the box is the 50th percentile (the median). The top and bottom lines indicate the minimum and maximum. Adjuvant treatment is given post-surgery; CT: Chemotherapy; RT: Radiotherapy; ET: Endocrine therapy

Fig. 4 Utility values for three health states stratified by treatment

Table 3 Quality appraisal of two studies for older women

No	Questions	Williams et al. (2011) [41]	Sattar et al. (2019) [45]
E1	Is an explanation provided for the choice of technique(s) used to elicit HSUVs?	Complete	Partial
E2	Is a comprehensive description provided of technique(s) used to elicit the obtained HSUVs?	Complete	Complete
E3	Is an explanation provided for the choice of the population used to elicit HSUVs (i.e., patient, healthcare professional [and type], expert, general population)?	Partial	Partial
E4	Is a comprehensive description provided for the population used to elicit HSUVs (i.e., characteristics, size, and nationality)?	Complete	Complete

Complete: Yes (complete); Partial: Yes (partial); E: elicitation

Appraisal questions extracted from the study by Nerich et al. (2017) [32]

our analysis, the finding is still informative for health care decision-making. First, the catalogue of EQ-5D values by Sullivan et al. [50] estimated an age-related utility decrement of -0.0003 in the general population. However, the results from this study indicate that the condition-specific age-related utility decrement for breast cancer has a larger magnitude (-0.0013) than for the general population. The validity of future studies designed to estimate the lifetime trajectory of HSUVs may improve by using condition-specific age-related utility decrements (as part of the base case or sensitivity analysis) instead of those values estimated from the general population. Second, the utility decrement associated with disease progression may be overestimated by omitting age as an independent variable (for example, compare the utility decrements for disease states across both regression specifications in Table 4). In comparison with other published results, the utility decrement of the progressed state compared with the stable state was -0.143 in Peasgood et al. [12] and -0.0549 in the present study. Similarly, the utility decrement of the advanced state was -0.338 in Peasgood et al. [12] and -0.1521 in the present study. There are two main reasons to explain the differences between these estimated decrements.

Table 4 Regression models for HSUVs

Variables	Estimated coefficient ± 95% CI			
	Age-adjusted		No age adjustment	
	Coefficient (95% CI)	*p* value	Coefficient (95% CI)	*p* value
Age	-0.001 (-0.004, 0.002)	0.502	-	-
Health state reference: stable state (*n* = 32)				
Progressed state (*n* = 10)	-0.052 (-0.097, -0.007)	0.027	-0.055 (-0.102, -0.008)	0.021
Advanced state (*n* = 8)	-0.143 (-0.264, -0.022)	0.02	-0.146 (-0.267, -0.024)	0.055
Instrument reference: EQ-5D-3L instrument (*n* = 43)				
EQ-5D-5L (*n* = 7)	0.176 (0.115, 0.237)	< 0.001	0.176 (0.120, 0.233)	0.025
Treatment reference: surgery alone (*n* = 3)				
Surgery adjuvant chemotherapy (*n* = 20)	0.205 (0.133, 0.277)	< 0.001	0.209 (0.144, 0.274)	0.029
Surgery adjuvant radiotherapy (*n* = 2)	0.200 (0.141, 0.259)	< 0.001	0.204 (0.157, 0.252)	0.021
Surgery adjuvant endocrine therapy (*n* = 5)	0.085 (0.036, 0.135)	0.003	0.085 (0.040, 0.131)	0.020
Surgery without specified adjuvant (*n* = 19)	0.107 (0.069, 0.144)	< 0.001	0.114 (0.084, 0.144)	0.013
Unspecified treatment (*n* = 1)	0.148 (0.081, 0.215)	< 0.001	0.136 (0.072, 0.200)	0.029
Valuation time reference: less than one year (*n* = 19)				
Over 1 year (*n* = 31)	0.045 (0.006, 0.083)	0.027	0.050 (0.012, 0.088)	0.017
Constant	0.696 (0.485, 0.908)	< 0.001	0.639 (0.575, 0.703)	0.029
Observations	50		50	
R-squared	0.691		0.686	

First, the review by Peasgood [12] included values measured using various preference-based instruments, while we only included HSUVs measured by EQ-5D. Second, Peasgood [12] analysed women with breast cancer in all age groups, whereas this review focused on postmenopausal women with early-stage breast cancer. Collectively, these reasons led to a smaller sample size for the meta-regression compared with other published examples. Consequently, the results from the regression model in the present study provide relevant HSUV decrements for postmenopausal women with early-stage breast cancer for decision-makers who use an EQ-5D instrument.

In addition, a growing phenomenon in managing breast cancer for older women is that many patients will receive primary endocrine therapy, instead of surgery, as their initial treatment [54–56]. Yet this review found no studies that estimated HSUVs for women with early-stage breast cancer who received non-surgical first-line treatment. Instead, the identified studies comprised patients who received surgery with or without adjuvant treatment. One study did not meet the inclusion criteria for this review (because HSUVs were measured using the EQ-5D-5L England tariff) but did measure HSUVs for older women receiving primary endocrine therapy [57]. The size of the patient cohort who receive non-surgical intervention in clinical practice is likely to increase, all else being equal, as the population ages and more breast cancer cases are diagnosed at a later age [55, 56]. A greater focus on estimating health utility values for this patient cohort will be valuable to better understand how HSUVs can be affected by the direct impact of treatment-related side effects and the longer-term impact of changes in disease outcomes.

One limitation of this review was related to the search process. The search strategy only identified published manuscripts from peer-reviewed academic journals and may have missed HSUVs reported in the grey literature and other data sources. However, the results indicate that the sample of included studies may be potentially sufficient to pool and quantify the condition-specific association between age and health utility for older women with breast cancer. Searching Medline and Embase has a high ability to identify relevant studies (Bramer et al. [58] report a 92.8% recall rate) and have been used effectively by other systematic reviews of HSUVs [59].

A second limitation was that only HSUVs measured by the EQ-5D instruments were included in the analysis. This may constrain the generalisability of the results because the estimated associations are not likely to apply to other preference-based instruments (such as the Short Form-6 Dimension [60] or the Health Utilities Index [61]). However, the focus on EQ-5D instruments will be most valuable to health

care decision-makers because of its widespread global use by health technology assessment bodies [15]. Finally, omitting the EQ-5D valuation tariff as an independent variable in the meta-regression is a limitation if these cross-country differences impacted the estimated mean HSUV. This impact could be explored further as more HSUVs for older women with breast cancer become available across different countries in the future.

Future research can aim to investigate the impact of age on HSUVs estimated by other preference-based instruments for older women with breast cancer, and identify studies from other data sources to supplement the current results. In addition, future studies can be designed to establish whether HSUVs estimated by EQ-5D instruments are affected by the treatment received once older patients enter the progressed or advanced disease states. Finally, other chronic conditions (such as diabetes and cardiovascular disease) are becoming more common due to an ageing population [62]. Future studies can estimate the condition-specific age-related utility decrement for different diseases to improve the validity of lifetime HSUV estimates and the quality of evidence that informs health care decision-making.

Conclusion

This study strengthens the HSUV evidence base to help inform future decision-making regarding older women with breast cancer. Analysts can use the data sources presented in this review to identify age-specific HSUV estimates that are most relevant for their decision-making context. The age-adjusted health utility decrements for disease states can improve the quality of crucial input parameter values for cost-effectiveness analyses of treatments for this older population. The estimated condition-specific health utility decrement will improve the validity of lifetime HSUV estimates for people with breast cancer. A greater emphasis on accounting for the impact of age on HSUVs will improve the robustness of evidence essential to guide health care decision-making for the growing number of older patients diagnosed with early-stage breast cancer.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12955-022-02067-w.

Additional file 1. Appendix 1. PRISMA 2020 Checklist. Appendix 2. Search Strategy for Databases. Appendix 3. Quality Appraisal Tool. Appendix 4. Reasons for Excluding Studies during Database Record Screening. Appendix 5. Data Extraction of the Mean Utility Values.

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Code availability
Not applicable.

Authors' contributions
All authors, Yubo Wang (YW), Sean P Gavan (SG), Douglas Steinke (DS), Kwok-Leung Cheung (KLC) and Li-Chia Chen (LCC), contributed to the study's conception and design. LCC led the project and developed research ideas. YW, SG, and LCC performed study design, data collection, and interpretation. YW wrote the first draft of the manuscript, and all authors commented on previous versions. All authors read and approved the final manuscript.

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Availability of data and materials
Supplement information is included in the appendices.

Declarations

Competing interests
Kwok-Leung Cheung has served in a consultancy capacity for Roche. All other authors (Yubo Wang, Sean P Gavan, Douglas Steinke and Li-Chia Chen) declare no conflict of interest.

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Publisher's Note

Appendix 9. Chapter 4: PRISMA 2020 checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction Line 106-110
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Method, inclusion and exclusion
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Method, Literature search
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Method, Literature search
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Method, Study selection
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Method, Data extraction
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Method, Data extraction

Section and Topic	Item #	Checklist item	Location where item is reported
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Method, Data extraction
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Method, Data synthesis Line 197
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Method, Data synthesis
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Method, Data synthesis
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Method, Data synthesis
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Method, Data synthesis
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Method, Data synthesis
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Method, Data synthesis
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Method, Data synthesis
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Method, Data synthesis
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not report
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Results, selection of studies

Section and Topic	Item #	Checklist item	Location where item is reported
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Results, selection of studies
Study characteristics	17	Cite each included study and present its characteristics.	Results, study characteristics
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Results, Quality appraisal of studies measuring HSUV in older women
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Results, study characteristics
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Results, Regression analysis
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results, Regression analysis
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not reported
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not reported
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not reported
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion
	23b	Discuss any limitations of the evidence included in the review.	Discussion
	23c	Discuss any limitations of the review processes used.	Discussion
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion

Section and Topic	Item #	Checklist item	Location where item is reported
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Method
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Method
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Method
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	End of study
Competing interests	26	Declare any competing interests of review authors.	End of study
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Appendices

Appendix 10. Chapter 4: Search strategy for databases

1. Embase from 2009 January to 2021 22 September

No	Searches
1	quality adjusted life year/
2	(quality adjusted or adjusted life year$).ti,ab,sh.
3	(qaly$ or qald$ or qale$ or qtime$).ti,ab,sh.
4	(illness state$1 or health state$1).ti,ab,sh.
5	(hui or hui1 or hui2 or hui3).ti,ab,sh.
6	(multiattribute$ or multi attribute$).ti,ab,sh.
7	(utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,sh.
8	utilities.ti,ab,sh.
9	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or European qol).ti,ab,sh.
10	(euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,sh.
11	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,sh.
12	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,sh.
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14	breast tumor/
15	exp breast/ or exp breast disease/
16	exp malignant neoplasm/
17	(cancer$ adj3 breast$).tw.
18	(neoplas$ adj3 breast$).tw.
19	(carcinoma$ adj3 breast$).tw.
20	(adenocarcinoma$ adj3 breast$).tw.
21	(tumour$ adj3 breast$).tw.
22	(tumor$ adj3 breast$).tw.
23	(malignan$ adj3 breast$).tw.
24	15 and 16
25	17 or 18 or 19 or 20 or 21 or 22 or 23
26	14 or 24 or 25
27	limit 26 to female
28	premenopause/

29	27 not 28
30	13 and 29
31	limit 31 from 2009 to current

2. Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 2009 January to 2021 22 September

No	Searches
1	Quality-Adjusted Life Years/
2	(quality adjusted or adjusted life year$).ti,ab,kf.
3	(qaly$ or qald$ or qale$ or qtime$).ti,ab,kf.
4	(illness state$1 or health state$1).ti,ab,kf.
5	(hui or hui1 or hui2 or hui3).ti,ab,kf.
6	(multiattribute$ or multi attribute$).ti,ab,kf.
7	(utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf.
8	utilities.ti,ab,kf.
9	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or European qol).ti,ab,kf.
10	(euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kf.
11	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf.
12	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf.
13	quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf.
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
15	exp Breast Neoplasms/
16	exp Breast/ or exp Breast Diseases/
17	exp Neoplasms/
18	(cancer$ adj3 breast$).tw.
19	(neoplas$ adj3 breast$).tw.
20	(carcinoma$ adj3 breast$).tw.
21	(adenocarcinoma$ adj3 breast$).tw.
22	(tumour$ adj3 breast$).tw.
23	(tumor$ adj3 breast$).tw.
24	(malignan$ adj3 breast$).tw.

25	16 and 17
26	18 or 19 or 20 or 21 or 22 or 23 or 24
27	15 or 25 or 26
28	Premenopause/
29	limit 27 to female
30	29 not 28
31	14 and 30
32	limit 31 from 2009 to current

Appendix 11. Chapter 4: Completed quality appraisal tool

Questions concerning	
Data source selection of HSUV used by authors of CUA	
S1.	What is (are) the data source(s) of HSUVs?
S2.	If HSUVs are derived from the literature, how many references are given?
S3.	If derived from the literature, what is (are) the data source(s) of HSUVs?
Elicitation of HSUVs used by authors of CUA	
E1a.	Is an explanation provided for the choice of technique(s) used to elicit HSUVs?
E1b.	Is a comprehensive description provided of technique(s) used to elicit the obtained HSUVs?
E2a.	Is an explanation provided for the choice of the population used to elicit HSUVs (i.e., patient, healthcare professional [and type], expert, general population)?
E2b.	Is a comprehensive description provided for the population used to elicit HSUVs (i.e., characteristics, size, and nationality)?
Use of HSUVs by authors of CUAs:	
U1.	Are the HSUVs appropriate with respect to comparability of populations (i.e., diagnosis and disease severity)?
U2.	Are the HSUVs appropriate with respect to comparability of countries?
U3.	Is the difference between when the CUA was performed and when the HSUVs were elicited less than 10 years?
U4.	Do the authors use specific utility values for each health state of the model in the CUA?
U5.	Do the authors use only a single source of utility values for each health state of the model in the CUA?
U6.	Do the authors use specific utility values for each of the compared interventions in the CUA?
U7.	Do the authors use the same HSUVs in the CUA as presented in the original data source?
U8.	Do the authors provide a comprehensive description and explanation for the explicit assumptions on the use of the HSUVs in the CUA?
U9.	Do the authors report results from a deterministic and probabilistic sensitivity analysis for the HSUVs?
U10.	Do the authors discuss the limitations of the data source selection, the elicitation, and the use of HSUVs in the CUA?

Appendix 12. Chapter 4: Data collection of the mean utility values

Study	Mean value	Standard deviation	States	Sample size	Mean age	Instrument	Treatment	Tariff	Measuring time
Conner-Spady, et al. (2005) [1]	0.79	0.19	Stable	45	45	EQ-5D-3L	Surgery +Chemo	UK	< 1year
Conner-Spady, et al. (2005) [1]	0.84	0.19	Stable	40	45	EQ-5D-3L	Surgery +Chemo	UK	< 1year
Conner-Spady, et al. (2005) [1]	0.84	0.13	Stable	36	45	EQ-5D-3L	Surgery +Chemo	UK	> 1 year
Conner-Spady, et al. (2005) [1]	0.89	0.13	Stable	37	45	EQ-5D-3L	Surgery +Chemo	UK	> 1 year
Etikasari, et al. (2021) [2]	0.584	0.44	Advanced	126	59.2	EQ-5D-5L	Surgery	Indonesian	> 1 year
Etikasari, et al. (2021) [2]	0.768	0.19	Progression	126	59.2	EQ-5D-5L	Surgery	Indonesian	> 1 year
Etikasari, et al. (2021) [2]	0.871	0.1	Stable	126	59.2	EQ-5D-5L	Surgery	Indonesian	< 1year
Freedman, et al. (2010) [3]*	0.89	0.33	Stable	1050	50	EQ-5D-3L	Surgery +Radio	USA	> 1 year
Freedman, et al. (2010) [3]*	0.9	0.66	Stable	1050	50	EQ-5D-3L	Surgery +Radio	USA	> 1 year
Kimman, et al (2009) [4]	0.72	0.29	Progression	23	55.8	EQ-5D-3L	Surgery without specified adjuvant	UK	> 1 year
	0.73	0.18	Progression	14	55.8	EQ-5D-3L	Surgery without specified adjuvant	UK	> 1 year
Kimman, et al (2009) [4]	0.71	0.2	Stable	72	55.8	EQ-5D-3L	Surgery without specified adjuvant	UK	> 1 year
	0.78	0.14	Stable	28	55.8	EQ-5D-3L	Surgery without specified adjuvant	UK	> 1 year
Kimman, et al (2009) [4]	0.82	0.21	Stable	55	55.8	EQ-5D-3L	Surgery without specified adjuvant	UK	> 1 year
	0.685	0.34	Advanced	345	57	EQ-5D-3L	Unspecified	UK	> 1 year
Kimman, et al (2009) [4]	0.779	0.12	Progression	345	57	EQ-5D-3L	Unspecified	UK	> 1 year
	0.779	0.2	Progression	345	57	EQ-5D-3L	Unspecified	UK	> 1 year

Kimman, et al (2009) [4]	0.696	0.535	Stable	345	57	EQ-5D-3L	Unspecified	UK	< 1year
	0.78	0.15	Stable	18	75.3	EQ-5D-3L	Surgery +Chemo	Canada	< 1year
Lidgren, et al. (2007) [5]	0.82	0.29	Stable	24	74.7	EQ-5D-3L	Surgery +Chemo	Canada	< 1year
	0.82	0.27	Stable	21	74.7	EQ-5D-3L	Surgery +Chemo	Canada	< 1year
Lidgren, et al. (2007) [5]	0.83	0.22	Stable	12	75.3	EQ-5D-3L	Surgery +Chemo	Canada	< 1year
	0.757	0.2	Stable	19	53.4	EQ-5D-3L	Surgery +Chemo	UK	< 1year
Lidgren, et al. (2007) [5]	0.791	0.16	Stable	19	53.4	EQ-5D-3L	Surgery +Chemo	UK	< 1year
	0.831	0.13	Stable	19	53.4	EQ-5D-3L	Surgery +Chemo	UK	< 1year
Lidgren, et al. (2007) [5]	0.882	0.14	Stable	19	56.7	EQ-5D-3L	Surgery +Chemo	UK	< 1year
	0.883	0.13	Stable	19	56.7	EQ-5D-3L	Surgery +Chemo	UK	< 1year
Sattar, et al. (2019) [6]	0.921	0.12	Stable	19	56.7	EQ-5D-3L	Surgery +Chemo	UK	< 1year
	0.686	0.57	Advanced	224	50.7	EQ-5D-3L	Unspecified	China	> 1 year
Sattar, et al. (2019) [6]	0.774	0.4	Advanced	556	49.1	EQ-5D-3L	Unspecified	China	> 1 year
	0.789	0.18	Stable	1234	49.8	EQ-5D-3L	Unspecified	China	> 1 year
Sattar, et al. (2019) [6]	0.792	0.34	Stable	498	49.1	EQ-5D-3L	Unspecified	China	> 1 year
	0.77	0.2	Stable	128	72.3	EQ-5D-3L	Surgery + Radio	UK	< 1year
Sattar, et al. (2019) [6]	0.78	0.2	Stable	126	72.8	EQ-5D-3L	Surgery +Endocrine	UK	< 1year
	0.85	0.45	Advanced	43	51.2	EQ-5D-5L	Unspecified	China	> 1 year
Tanaka, et al. (2019) [7]	0.94	0.17	Progression	258	52.7	EQ-5D-5L	Unspecified	China	< 1year
	0.92	0.63	Progression	20	49.9	EQ-5D-5L	Unspecified	China	> 1 year
Tanaka, et al. (2019) [7]	0.89	0.24	Stable	125	51.4	EQ-5D-5L	Unspecified	China	> 1 year
	0.552	0.23	Advanced	24	46.7	EQ-5D-3L	Unspecified	UK	> 1 year
Tanaka, et al. (2019) [7]	0.73	0.22	Progression	71	46.7	EQ-5D-3L	Unspecified	UK	> 1 year

	0.718	0.14	Progression	15	46.7	EQ-5D-3L	Unspecified	UK	> 1 year
Tanaka, et al. (2019) [7]	0.674	0.2	Stable	48	46.7	EQ-5D-3L	Unspecified	UK	< 1year
	0.862	0.11	Stable	39	48.9	EQ-5D-3L	Surgery +Chemo	Korea	< 1year
Tanaka, et al. (2019) [7]	0.902	0.08	Stable	92	49.1	EQ-5D-3L	Surgery +Chemo	Korea	< 1year
	0.909	0.09	Stable	149	49.5	EQ-5D-3L	Surgery +Chemo	Korea	> 1 year
Tanaka, et al. (2019) [7]	0.919	0.09	Stable	226	53.6	EQ-5D-3L	Surgery +Chemo	Korea	> 1 year
	0.924	0.08	Stable	180	49.5	EQ-5D-3L	Surgery +Chemo	Korea	> 1 year
Wang, et al. (2018) [8]	0.62	0.34	Advanced	32	54	EQ-5D-3L	Unspecified	UK	> 1 year
	0.78	0.16	Progression	49	56.2	EQ-5D-3L	Unspecified	UK	> 1 year
Wang, et al. (2018) [8]	0.85	0.17	Stable	33	44.7	EQ-5D-3L	Unspecified	UK	> 1 year

Reference A11

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Appendix 13. Chapter 5: CHEERS 2022 Checklist

Topic	No.	Item	Location where item is reported
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	Title
Abstract	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Abstract
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Introduction
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	Methods
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Methods
Setting and location	6	Provide relevant contextual information that may influence findings.	Methods
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Methods
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Methods
Time horizon	9	State the time horizon for the study and why appropriate.	Methods
Discount rate	10	Report the discount rate(s) and reason chosen.	Method
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Methods, Data analysis section
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Methods, Clinical effectiveness section
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Methods, utility section
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Methods, Resource use and cost section
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Methods, Resource use and cost section
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Methods, Model structure & Figure 1
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Methods

Topic	No.	Item	Location where item is reported
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Methods, Clinical effectiveness section
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	Methods, Clinical effectiveness section
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	Methods, Data analysis section
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	Not reported
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Results
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Results, Deterministic base-case analysis
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Results, Sensitivity analyses
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, public, community, or stakeholder involvement made to the approach or findings of the study	Results, Value of information analysis & Value of implementation analysis
Discussion			
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Discussion
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Not reported
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Not reported

Appendix 14. Chapter 5: Estimating time to death and progression

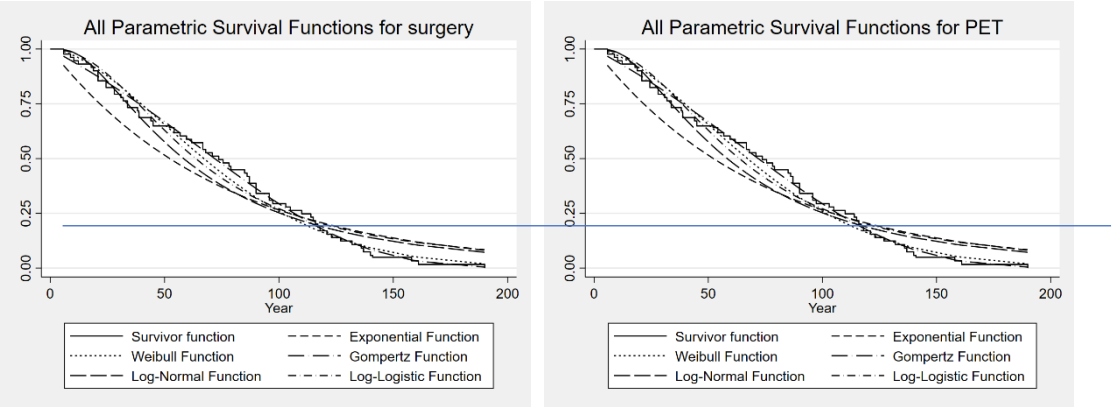
Parametric survival analysis was used to extrapolate the overall survival for surgery and PET separately, assuming about the risk of death change over time and estimating the survival functions and probability functions at a particular time point [1, 2]. A randomised control trial was used to identify the survival probabilities for older women with primary breast cancer receiving surgery and primary endocrine therapy with 20 years of observation since the trial started in the early 1980s.

The five parametric survival curves described (exponential, Weibull, Gompertz, log-logistic, log-normal) fit these survival data. The parametric survival curve used to simulate time to death in the decision-analytic model was chosen according to the lowest AIC and BIC statistics and by visual inspection to ensure the biologic plausibility of the estimated survival curve. All analyses were performed in STATA Version 14.

A14.1 Results

The Kaplan-Meier curves of initial surgery and PET for all-cause mortality and time to progression were plotted separately.

Figure A14. 1 Kaplan-Meier curves of surgery and PET for all-cause mortality



(Note) The left figure is the curve plotted for the initial surgery, and the right figure is the curve for the PET.

Table A14. 1 Parametric survival distribution of surgery for all-cause mortality

Parameter	Exponential	Weibull	Gompertz	Log-normal	Log-logistic
Rate	-1.83				
Shape		-3.17	-2.65	1.56	1.65
Scale		0.49	0.16		0.46
Location				0.82	
AIC	333.52	297.05	293.77	323.76	324.56
BIC	336.39	302.79	299.52	329.51	330.31

Table A14. 2 Parametric survival distribution of PET for all-cause mortality

Parameter	Exponential	Weibull	Gompertz	Log-normal	Log-logistic
Rate	-1.94				
Shape		-3.21	-2.38	1.70	1.72
Scale		0.45	0.082		0.41
Location				0.73	
AIC	331.58	298.54	317.03	295.99	294.37
BIC	334.45	304.29	322.78	301.74	300.12

The Gompertz survival curves had the lowest AIC and BIC test statistics of surgery, and Log-logistic had the lowest AIC and BIC test statistics of PET, indicating that it fits the observed data best. Therefore, the decision-analytic model used a Gompertz survival curve of surgery and a Log-logistic survival curve of PET to estimate the time to death.

Figure A13. 2 Kaplan-Meier curves of surgery and PET for time to progression

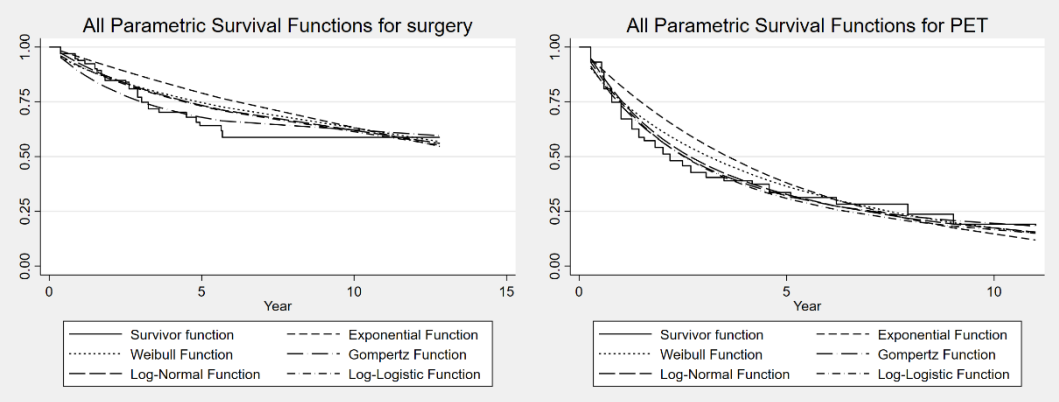


Table A13. 3 Parametric survival distribution of surgery for time to progression

Parameter	Exponential	Weibull	Gompertz	Log-normal	Log-logistic
Rate	-3.27				
Shape		-2.74	-2.59	3.16	3.1
Scale		-0.25	-0.14		1.12
Location				1.96	
AIC	307.12	305.48	297.97	299.30	302.94
BIC	309.99	311.23	303.72	305.05	308.69

Table A13. 4 Parametric survival distribution of PET for time to progression

Parameter	Exponential	Weibull	Gompertz	Log-normal	Log-logistic
Rate	-2.11				
Shape		-1.22	-0.57	1.7	1.26
Scale		-0.61	-0.62		1.3
Location				0.73	
AIC	460.10	453.29	440.34	431.15	436.52
BIC	462.97	459.04	446.09	436.90	442.27

The Gompertz survival curves had the lowest AIC and BIC test statistics of surgery, and Log-normal had the lowest AIC and BIC test statistics of PET, indicating that it fits the observed data best. Therefore, the decision-analytic model used a Gompertz survival curve of surgery and a Log-normal survival curve of PET to estimate the time to progression.

Appendix 15. Chapter 6: ISAC protocol

Applicants must complete all sections listed below Applications with sections marked 'Not applicable' without justification will be returned as invalid
A. Study Title (Max. 255 characters, including spaces) Examining the clinical and economic outcomes associated with cancer survivorship
B. Lay Summary (Max. 250 words) Due to improvements in cancer diagnosis and medical care, nowadays many patients who experience cancer survive and live to an older age. However, some smaller-scale studies suggest that people who survive cancer are more likely to experience other health problems (such as bone fractures or develop diabetes). Due to the ageing population, there is also an increasing number of patients diagnosed with cancers at an older age. It is also unclear whether older people with cancer should be treated in the same way as younger people, or whether other treatments are more beneficial for older cancer patients. Therefore, this study aims to find out how experiencing cancer affects the chances of developing other health problems by comparing the occurrence of these events between cancer survivors to individuals without a history of cancer. We also plan to examine the effects and related costs of different treatments for patients with breast cancer or lung cancer and compare the results between older and younger cancer patients.
C. Technical Summary (Max. 300 words) With advances in cancer diagnosis and treatments, the life expectancy of people who experience cancer has significantly increased but the epidemiology of other chronic diseases after cancer treatment and associated the risk factors is still under-studied. In addition, an increasing number of patients are diagnosed with cancer at an older age (e.g. breast cancer) due to the ageing population and the growing innovative treatments applied to cancer care (e.g. for lung cancer) have resulted in marked increases in healthcare costs. Examining the clinical- and cost-effectiveness of different treatment strategies for cancer considering the age and cancer staging of patients will help to inform the future development of treatment stratification tools to optimise cancer treatments. This study aims to investigate the risk of bone fracture and endocrine disorders in patients surviving following the treatments of site-specific cancers and evaluate the treatment pathways and medical resource use in adult patients with lung and breast cancer. A retrospective matched cohort study design will be used to compare the incidence of bone fracture and endocrine disorders in cancer survivors, and their age, gender and practice-matched controls (1:5 matching) and the association between different site-specific cancers and risks of bone fracture or endocrine disorder events will be estimated. Cox proportional hazard models will calculate the hazard ratios for each outcome, comparing survival in cancer survivors and control patients. For those cohorts of patients with breast or lung cancers, we will examine other clinical outcomes (all-cause mortality and cancer-specific mortality, survival time) and health resource use taking account of different treatment strategies. Cox proportional hazards models will be used to analyse the mortality outcomes, and generalised linear models will be used to analyse the costs by adjusting for relevant factors, such as cancer staging. The results will provide evidence to inform clinical decision-making to treatment optimisation for cancer patients.
D. Outcomes to be Measured The primary outcome of this study is the incidence of mortality and morbidity associated with cancer (e.g. cancer-related and all-cause mortality; cancer progression, recurrence or metastasis of cancer) or development of other specific conditions, namely bone disorders (fractures, osteoporosis, osteopenia); diabetes and endocrine disorders (hypopituitarism, adrenal failure (Addison's), Adrenocorticotropic hormone (ACTH) deficiency, hypogonadism, hypothyroidism). The secondary outcomes of interests include the treatment strategies for patients with either breast or lung cancer (i.e. initial and subsequent treatments and the combinations of different treatment strategies), treatments for concomitant conditions, and medical resources use (e.g. referral, admission to accident and

emergency; all-cause hospitalisation; secondary care outpatient visit; primary care visit; medicine prescriptions).

E. Objectives, Specific Aims and Rationale

This project aims to investigate the risk of clinical outcomes and medical resource use in adults with site-specific cancer. The objectives include:

1. To quantify the absolute and relative risks of bone and endocrine disorders in survivors of the 20 most common site-specific adult cancers.
   - To examine the extent to which relative risk differences are driven by shared risk factors, demographic characteristics, and use of chemotherapy and radiotherapy.
2. To evaluate the clinical outcomes and medical resource use in adult patients with lung and breast cancers
   - To describe the treatment pathways of patients with lung and breast cancers by different initial treatment strategies, and to identify the outcomes of breast and lung cancers (e.g. mortality and disease progression);
   - To estimate the medical resource use and associated costs of treatment in primary care and secondary healthcare settings;
   - To examine the association among risk factors, clinical outcomes of cancer treatments, and medical resource use in patients with lung and breast cancers.

With the advance in biomedical technologies and cancer care, the overall survival of people with cancer has increased markedly in the UK [1]. However, overall survival after cancer in the UK is still low compared with other European countries, particularly for lung and breast cancers. To optimise cancer care, factors associated with poor cancer prognosis need to be investigated in terms of (1) understanding the disease epidemiology and characteristics of the population, (2) considering the access and adherence to different treatment regimens, and the influence of multimorbidity, and (3) examining both cancer-related prognosis and outcomes of other (non-cancer) diseases during the cancer survivorship. In addition, we plan to further focus on two major cancers (breast and lung cancer), which have high prevalence and profound implications for healthcare resource use, to investigate the impact of ageing and cancer-staging on treatment outcomes and healthcare costs. The results of this study will be used in evaluating the cost-effectiveness of treatment stratification tools and developing a risk management plan for cancer survivors with long-term conditions, and hence, will inform the optimisation of cancer care to enhance cancer survivorship.

F. Study Background

The landscape of cancer care has changed significantly in the past two decades due to the advances in diagnostic technologies, innovative treatment and public health promotion strategies. Cancer is a common condition; people born after 1960 have a 50% chance of developing cancer during their lifetime [2]. With the significant advance in the technology for cancer diagnosis and treatment, the overall survival of people with cancer has increased markedly in the UK and other parts of the world [3]. Although the survival of cancer in the UK is still low compared with other European countries [4], cancer survival rates in the UK have improved markedly over recent decades. However, the survivor rate and duration are low for patients residing in most deprived areas in the UK [5], and this may be due to other health conditions (multi-morbidity) and health literacy (delaying access to health care) [6-8].

Pharmacotherapy and/or radiotherapy are the mainstay of cancer treatment [9, 10]. New treatment strategies involving 'targeted therapy' or combining novel immune-oncology with conventional chemotherapy treatments are increasing [11-13]. These new treatment strategies have not only improved patient outcomes but also increased costs to the healthcare system substantially [14, 15]. Several risk-stratified screening programmes and treatment stratification tools have been developed to optimise the use of high-cost cancer treatments [16, 17]. However, these risk-stratification tools have not been validated at a population level and adjusted for relevant confounders (e.g. cancer stage, Nottingham prognostic index (NPI) for breast cancer, Eastern Cooperative Oncology Group (ECOG) performance status and comorbidity) to inform the clinical and cost effectiveness outcomes of innovative treatment strategies [18].

Nowadays, many cancers can be controlled and managed for long periods [19]. Therefore, adherence to long-term treatment and outcome monitoring has become increasingly important during cancer survivorship [20, 21] particularly for those patients with multimorbidity. There is little understanding about how patients undergoing complex treatment regimens for cancer adhere to their medicines. A population-based cohort study has demonstrated that survivors of most site-specific cancers had increased medium-term to long-term risk for one or more cardiovascular diseases compared with that for the general population [22]. There is also some evidence suggest that exposure to cancer treatments may influence the incidence of other chronic conditions (e.g. bone disorders, diabetes and other endocrines disorders) or non-cancer related mortality [22-25]. Furthermore, several research also indicates that exposure to long-term medication, such as aspirin, statins and metformin may reduce the risk of developing cancer [26-28].

In addition, due to the ageing population, an increasing number of people with cancer diagnoses are at an older age, such as breast cancer [29]. The optimisation of routine cancer treatments for older patients is a challenging issue as most of the older population, particularly those with frailty, multimorbidity and polypharmacy, are commonly excluded from randomised controlled trials [30, 31] and current treatments for older patients with cancer generally follow the clinical guideline based on evidence deriving from younger populations [32-35]. Older women with primary breast cancer have a higher level of oestrogen receptor positivity compared with younger women. Hence primary endocrine therapy is more likely to be successful for older women with breast cancer [36]. Nevertheless, the impact of ageing (or frailty) on the utilisation and combination of different treatments is unclear, and whether the current conventional physical (tumour size, pathological clinical response), clinical outcomes (e.g. overall survival, disease-free survival) are the optimal measures to determine the effectiveness of treatment for this population.

The main research questions of this study include:

(1) What is the incidence of conditions, non-cancer specific morbidities, and cancer-specific outcomes in adult patients with site-specific cancer? How does the risk of non-cancer specific morbidities (bone fracture and endocrine events) differ between people with and without cancer? And do other risk factors or exposure to long-term medicines (aspirin, statins and metformin) influence the risk of developing the above outcomes?

(2) What are the treatment patterns (initial and subsequent treatments, single or combined therapy) for adult patients with site-specific cancer (i.e. lung and breast cancer)? How does age influence the treatment of cancer? And what are the generic (overall survival, disease-free survival) and cancer-specific outcomes (progression, recurrence), resource use and costs associated with different initial treatment strategies for patients with lung or breast cancer?

G. Study Type

This project is a descriptive/hypothesis generating study.

H. Study Design

Retrospective matched cohort study design to compare the incidence rates of primary outcomes (Section 0) related to chronic conditions in adults with site-specific cancers. In addition, two subgroups of cohorts, i.e. patients with breast or lung cancer will be further followed for assessing the primary and secondary outcomes.

I. Feasibility counts

In a recently published literature, Strongman et al. (2019) reported there were 153,552 cancer survivors up to January 2014 CPRD Gold data, and the number of survivors by cancer site was sufficient to measure the anticipated number of cardiovascular events from the linkage data including CPRD Gold, Cancer Registry (NCRAS), HES-APC and ONS databases and linked data sources covered England only between 1st January 1990 and 31th December 2015 [22]. We will take a similar approach to Strongman et al. (2019) but use both CPRD Gold and Aurum with a linkage to NCRAS, HES-APC and ONS databases for a longer study period (1st January 2000 to 31st December 2016), and hence we are confident to enrol enough subjects for the cohort in this study. (sample size consideration)

J. Sample size considerations

As this is a hypothesis-generating study, a formal power calculation will not apply. In addition, we anticipated the number of events and the expected hazard ratio to conclusively detect for each cancer outcome pairing are like the study reported by Strongman *et al.* (2019). Similarly, both statistically precise and imprecise effect estimates will be presented to inform the overall patterns and helping to generate hypotheses; imprecisely estimated associations will be presented with appropriate caution.

We have attached a table of the incidence cancer counts (for the 20 most common cancer sites) in CPRD GOLD and Aurum during 2000-2016. The table also contains the number and percentage that were still under follow-up after 1 year following their incident diagnosis and the median follow-up for those patients. Obviously these are cases that have been identified via their primary care records - the numbers will be substantially augmented when we have the linked secondary care and cancer registry data.

	GOLD				**Aurum**			
	Incident cases	**Incident cases with follow-up > 1 year**			**Incident cases**	**Incident cases with follow-up > 1 year**		
Cancer site	***N***	***n***	**%**	**Median follow-up (yrs)**	***N***	***n***	**%**	**Median follow-up (yrs)**
Bladder	5103	3733	73.2	4.2	19,227	14,553	75.7	4.7
Brain/Central nervous system	1786	622	34.8	2.7	7030	2803	39.9	2.6
Breast	19,621	16,560	84.4	5.0	74,597	64,424	86.4	5.5
Cervix	2174	1780	81.9	4.8	5829	4741	81.3	5.4
Colorectum	12,400	8559	69.0	4.0	44,807	31,736	70.8	4.2
Kidney	1522	956	62.8	3.8	7656	5177	67.6	4.1
Leukaemia	3644	2390	65.6	4.2	13,189	9260	70.2	4.7
Liver	1303	361	27.7	2.0	5221	1654	31.7	2.1
Lung	11,246	3122	27.8	1.9	42,052	13,845	32.9	2.0
Malignant melanoma	5140	4270	83.1	4.6	20,255	17,212	85.0	5.1
Multiple myeloma	1743	1125	64.5	3.4	6503	4476	68.8	3.4
Non-Hodgkin lymphoma	4170	2955	70.9	4.4	16,033	11,801	73.6	4.6
Oesophagus	3396	1277	37.6	2.0	12,001	4838	40.3	2.0
Oral cavity	958	674	70.4	3.4	3280	2381	72.6	4.2
Ovary	2248	1446	64.3	3.2	9440	6590	69.8	3.7
Pancreas	2737	499	18.2	1.8	9365	2129	22.7	1.8
Prostate	16,301	13,508	82.9	4.3	60,122	50,921	84.7	4.9
Stomach	1920	716	37.3	2.3	7483	3145	42.0	2.5
Thyroid	888	725	81.6	5.2	3316	2711	81.8	5.2
Uterus	2362	1920	81.3	4.7	8153	6655	81.6	5.2

The counts are restricted to patients who are eligible for linkage (set 17) and patients that feature in both GOLD and Aurum (due to practice migration) have been removed from the GOLD data.

K. Planned use of linked data (if applicable):

This study will use the primary care date from CPRD Gold and Aurum, and data linkage will be requested for :

1. NCRAS Cancer Registration Data, Systemic Anti-Cancer Treatment (SACT) and National Radiotherapy Dataset (RTDS): National cancer registry will be used to identify the study cohort and will provide additional information about the stage, grade and treatment of cancer. In addition, SACT and RTDS will be used to identify the specific treatment regimens.
2. Hospital Episode Statistics Admitted Patient Care (HES-APC), Outpatient (HES-outpatient), and Accident and Emergency data (HES-A&E): The HES data will be used to identify outcome of interest including bone disorders, endocrine disorders, events related to cancer progression.
3. Office for National Statistics Death Registration Data: ONS death data provided the cause of death and hence will be used to ascertain the date of death and identify cancer-related or other causes of deaths.
4. Index of multiple deprivation (IMD) data: Patient-level socioeconomic status reported by IMD and the domains of IMD will be used as a covariate in planned analyses.

The use of linked data will improve ascertainment for cancer, bone fracture and endocrine events, and provide detail on cancer stage, grade and treatment. In contract, it will restrict the sample to patients registered in those practices that are eligible for data linkage. Therefore, sensitivity analyses will be carried out to identify if this restriction/improved ascertainment alters estimates. Besides, some secondary analyses will be conducted in which linkage is required (Section O). In these analyses where data linkages are applied, the samples will be restricted to those eligible for the relevant data linkages and take account of the relevant linkage coverage dates.

Our research will help inform the health service in determining which individuals are most likely to be at risk of experiencing longer-term complications following the treatment of cancer. Besides, the clinical- and cost-effectiveness findings will help to develop clinical guidelines to optimise patient care and inform public health policy.

L. Definition of the Study population

The study population are adults (>18 years old) with 20 of the most common site-specific cancers, i.e. individuals who have at least one cancer diagnosis recorded in either CPRD Gold/Aurum or HES-APC or the NCRAS-CRD from 2000 to 2016. Patients with site-specific cancer will be identified from CPRD Gold and Aurum by systematically screening the relevant Read code and SNOMED codes (Appendix 1) or the ICD-9-10 codes in the HES-APC or NCRAS Cancer Registration Data (Appendix 1). The date of the first-ever record of cancer diagnosis will be defined as the index date. Patients who are aged less than 18 years on the index date of cancer will be excluded.

Additional inclusion criteria will be applied to select the study cohort which fits the purpose of different study objectives. To investigate the incidence of bone and endocrine disorders in cancer survivors (Section E, Objective 1), patients who have no history of these events of interest and have more than 12-month follow-up period after the index date will be included in the study. Their matched controls will also be selected from patients without site-specific cancer (Section M). To evaluate the mortality outcomes and medical resource use, adults with lung and breast cancer (Section E, Objective 2) will be examined, who are excluded if they are registered via Death Certificate Only. Furthermore, to consider additional information on medical resource use, the subgroup of patients whose SACT data (January 2014 to September 2017) and RTDS (April 2012 to September 2017) are available, will be selected to measure the exposure to chemotherapy and radiotherapy. The linked data of study cohorts (Section K) will be followed from the index date to the date of death, the end of registration or the end of study (31st December 2016), whichever comes first.

M. Selection of comparison group(s) or controls

To investigate the incidence of bone and endocrine disorders (Section E, Objective 1), the study cohort (i.e. adults with 20 site-specific cancers) will be matched to up to 5 controls on the index date. Patients who (1) had no record of cancer (2) had at least 12-month follow-up period after index date, will be identified and matched to the study cohort by age (as near and possible and within ±3 years), sex, and GP practice [22].

To assess the treatment outcomes and medical resource use (Section E, Objective 2), the outcome measures of the two specific sub-treatment cohorts, i.e. adults with lung or breast cancer will be compared between different initial treatment strategies.

N. Exposures, Outcomes and Covariates

Exposure

To investigate the incidence of bone fracture, endocrine disorders (Section E, Objective 1), 20 site-specific cancer will be regarded as the exposure, including bladder, breast, cervical, central nervous system, colorectal, gastric, kidney, laryngeal, leukaemia, liver, lung, melanoma, myeloma, non-Hodgkin lymphoma, oesophagus, oral, ovary, pancreas, prostate, testicular, thyroid, uterus cancer.

To evaluate the clinical outcomes and medical resource use in adults with lung and breast cancer (Section E, Objective 2), the different initial treatment strategies, such as surgery, chemotherapy, radiotherapy, endocrine therapy, immunotherapy, biological (targeted) therapy etc., will be identified from the NCRAS Cancer Registration Data (Appendix 6). The treatment will be further categorised as primary or adjuvant treatment, or single or combination treatment by the time of treatment. In the subgroup of patients whose NCRAS-SACT data (January 2014 to September 2017) or NCRAS-RTDS (April 2012 to September 2017) are available, the exposure to chemotherapy and radiotherapy will also be retrieved from the databases.

Outcome

For objective 1 of this study, the outcomes will be incident diagnoses of bone disorders (fractures, osteoporosis, and osteopenia) and endocrine disorders (hypopituitarism, adrenal failure (Addison's), ACTH deficiency, hypogonadism, hypothyroidism, diabetes) identified by relevant ICD and Read codes from the general practice and hospital records (Appendix 1). The prescriptions of medicines for managing the conditions will also be retrieved as a proxy for determining the events.

For objective 2 of this study, the primary outcome includes the mortality and progression associated with cancer (e.g. cancer-related death; progression, recurrence or metastasis of cancer) or the mortality or morbidity related to other concomitant chronic conditions in adults with either lung or breast cancer. The follow-up duration (observation time in this study will be the period between earliest diagnosis and death or end of study window), mortality and time to mortality will be identified from each patient record using the linked ONS mortality records. The causes of mortality will be retrieved from the ONS Death Registration Data. Cancer recurrence and progression will be identified from the HES-APC data by applying a proxy measure suggested by Ricketts et al. (2014) [37]. The metastasis of cancer is defined as a diagnosis of secondary cancer recorded in the HES-APE, HES-outpatient or HES A&E.

The secondary outcomes of interests include the event and time of treatment strategies for cancer; treatments for concomitant conditions; and medical resources use. The initial event and time of treatments for cancers will be identified from the NCRAS Cancer Registration Data, and the NCRAS-SACT and NCRAS-RTDS and will also be explored to extract treatment information (Appendix 5). Surgery procedure will be further identified in HES-APE by OPCS-4 code (Appendix 2). Primary or subsequent treatments will be differentiated by the recorded date of treatment. In addition, primary tumour code and different sites of radiotherapy treatment (from NCRAS-RTDS) will be retrieved to differentiate the episodes according to the treatment sites for lung and breast cancers.

All records of the cohort's visits to primary (general practice visit; medicine prescriptions) and secondary care (e.g. attendance at accident and emergency; all-cause hospitalisation; secondary care outpatient visit) during the study period will be identified as medical resource use. Unit costs of primary care episodes and monitoring tests will be derived from the Personal Social Services Research Unit. A primary care episode will be defined as any event recorded in the consultation file over the course of the study period; adjustments will be made for duration and comorbidities. Unit costs of hospital inpatient and day-care will be derived from standard reference costs based on Healthcare Resource Group (HRG) case-mix and adjusted for length-of-stay. Number of cycles, dose (i.e. actual dose and adjusted dose) will be used to cost the chemotherapy treatments

In addition, the event of treatment review will be measured using the cancer care review (CCR) code, identified from the medical file of CPRD records. Number of CCRs received and the initiation lag time of CCR (from index date to the date of the first CCR) will also be measured. Although CCR data is only available in CPRD from 2005 onwards and may not be widely collected due to Quality Outcomes Framework (QOF) incentivisation only applying to CCRs conducted within six months of diagnosis, it may still provide some insight into treatment review practices to supplement understanding of the treatment pathway for breast cancer survivors.

Covariates

Patient characteristics including baseline age (at index date), sex, ethnicity, social-economic status (IMD), comorbidity (chronic conditions), mode of detection (from screening or primacy care referral) and cancer characteristics (cancer stage specified by T, N, M stages, tumour morphology and behaviour, oestrogen/progesterone receptor status, HER2 status, axillary nodal involvement, NPI score, ECOG) will be identified [38]. Screening status and routine of diagnosis (from NCRAS Cancer Registration Data) will be used to determine the mode of detection which will differentiate resource incurred from screening programme or clinical presentation. Oestrogen/progesterone receptor scores (from NCRAS Cancer Registration Data) will be used to justify the effectiveness of endocrine therapy for female breast cancer. Comorbidities for each patient will be identified from the medical file using the list of Read codes adapted by Crooks et al. (2016) [39]. The Charlson comorbidity index (CCI) scoring will then be applied to calculate a total weighting of comorbidities for each patient based on mortality risk and health care resources use. Means and ranges for comorbidity frequency and CCI score will be analysed. A Frailty Risk Score [40] which was originally developed from electronic hospital records to apply in observational studies, will be used to summarise the influence of age and multi-morbidity (polypharmacy) on frailty.

O. Data/ Statistical Analysis

For objective 1, Cox regression models will be used to estimate unadjusted and adjusted hazard ratios for each outcome of interest comparing cancer survivors and control patients. Initially, we will only account for the matching factors (unadjusted models), and then subsequently adjusting for covariates (Section N) to investigate the extent to which associations are driven by shared risk factors and other confounders. Separate models will be fitted for each cancer site and will account for the matched design by stratifying on the matched sets, allowing for a different baseline hazard function for each matched set, but with common covariate effects. The proportional hazards assumption will be assessed by fitting interactions with time since the index date and, if necessary, time-stratified effect estimates will be presented.

The differing effect of cancer history on the events of interest between subsets of the population will be estimated by fitting interactions with age group, sex (for cancers affecting both genders), smoking status, body mass index category, pre-existing events of interests (at index date), and deprivation category. As we will be using the date of cancer diagnosis as our index date for follow up, we will examine the extent to which this date has been imputed. This will allow us to conduct sensitivity analyses in which we exclude those cases having imputed dates from our analysis if we observe a modest proportion of cases are identified via imputed diagnosis dates.

To calculate cumulative incidence whilst accounting for competing risks, the competing risk of death due to causes other than the outcome of interest will be addressed using censoring, (thus estimating the cause-specific hazard and providing a causal interpretation assuming appropriate adjustment for confounding). The cumulative incidence of each outcome will be determined in the presence of competing risks, to evaluate the actual public health burden attributable to the outcomes of interest in the cancer survivor population.

For objective 2, descriptive statistics will be used to describe the demographic and disease characteristics of adult patients with lung or breast cancer and the prevalence of concomitant comorbidities in these patients. The cohorts' demographics (age, gender), cancer-specific characteristics, follow-up duration mortality and time to mortality will also be presented. The proportion of patients who received each of the most common treatments will be calculated.

The proportion of observed clinical outcomes will also be estimated and presented in a decision tree framework. These results will be stratified by age and type of cancer. Survival data will be displayed using a Kaplan-Meier curve [41] and stratified according to age group. Time-to-event analyses will be conducted to explore the relationship between patient factors (e.g. age at diagnosis, ethnicity, and comorbid status) and the occurrence of events over time using Cox regression models.

Generalized linear models [42] will be used to analyse the non-normally distributed health care resource use associated with cancer by adjusting for relevant covariates (e.g. age, tumour grade, cancer behaviour, mode of detection, treatments) selected using a stepwise backward elimination approach. All data will be

managed and analysed in STATA 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

P. Plan for addressing confounding

Confounding by age, sex and GP practice will be addressed by matching of exposed and unexposed patients on these factors. Age will also be included as a covariate if controls cannot be matched to the same birth year. In addition, variables assumed to be confounders will be included as covariates in the analyses (Section N).

Q. Plans for addressing missing data

For the exposure and outcome variables and some covariates in this study, the presence or absence of code will be used to assign patients to one of two groups. The absence of code is assumed to mean the condition is not present, so missing data (i.e. incorrectly absent codes) will not be identifiable, and thus cannot be addressed as part of the study.

For some covariates in the primary care data, there will be some explicitly missing data, such as the information for quantifying prescription medication (e.g. numeric daily dose or instructions for frequency of administration). The recording of these variables is unlikely to be conditionally independent of the variable values themselves in the primary care setting, so would not satisfy the assumption of missing at random for multiple imputations. The assumption made for complete case analysis – that the probability of a variable value being missing is independent of the outcome given the variable value, and other covariates in the model being fitted – is more likely to be met [43]. Therefore, complete case analysis (concerning variables not set by the presence or absence of code) will be conducted. If there are large amounts of missing data (>30%) then we will also conduct sensitivity analysis under a range of non-random missingness mechanisms.

In the linked cancer registry data, there may be some missing data in cancer stage, grade and treatment variables. Missingness in these variables will be described, and analyses of effect modification/mediation by these variables will be restricted to matched sets in which these data are complete for cancer exposed patient.

R. Patient or user group involvement

The research questions or the outcome measures were informed by previous research, the Lead Applicant conducted involving focus groups involving patients with cancer to identify their healthcare needs, access to services and medicine use problems, and the findings emphasised important issues regarding choices of treatment for older people with cancer, adherence to long-term treatments and other medication use problems related to polypharmacy and multi-comorbidity, which have been highlighted in the study background (Section F). Also, we engaged with clinical experts in cancer care in developing the research questions and designing the study. We plan to liaise with patient groups at the Christie Hospital in Manchester to help with dissemination of our study findings.

S. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

Results will be distributed by publication via conference presentations, posters and peer-reviewed scientific journals. We will ensure that the confidentiality is maintained during the analysis and reporting the results. No cell count contains less than 5 events will be reported in the finding and we will apply secondary suppression to protect these counts if needed.

Conflict of interest statement

- DMA reports research funding from AbbVie, Almirall, Celgene, Eli Lilly, Novartis, UCB and the Leo Foundation outside the submitted work.
- LCC receives research funding from Mundipharma Research Ltd. outside the submitted work.
- No other conflicts of interest to be declared.

T. Limitations of the study design, data sources, and analytic methods

Although this study will involve use of linked CPRD data sources, there are still inherent limitations with the databases as they were not established for research purposes. For example, in terms of the exposure, medication in the secondary care setting is not available, and the NCRAS-SACT only available from 2014 to 2017, and the progression information related to chemotherapy is generally incompletely recorded. Therefore, we plan to conduct subgroup analyses based on the availability of data. In terms of the cancer-related outcomes, such as progression or recurrence, these may not be fully recorded as well, and we will conduct sensitivity analysis to test the robustness of our results.

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V. List of Appendices

Appendix 1. Codes for identifying patients with sites-specific cancers diagnosis in CPRD Gold and Aurum.

To identify cancers in CPRD Gold and Aurum, the dictionary of Read codes and SNOMED code was systematically searched to find cancer-related codes using the keywords/word fragments below. The codes picked up by this search were then screened and those indicating malignancy were identified and classified by cancer type (done by Alex Trafford, reviewed by Matthew Carr).
Words and word fragments used to search Read code dictionary for cancer-related terms
MALIGN; NEOPL; CANCER; CARCINOMA; LYMPHO; BLASTOMA; MELANOMA; GLIOMA; SARCOMA; MYCOSIS FUNGOIDES; SEZARY; MYELOM; LEUKAE; MALIG; NEOP;

Appendix 2. Codes for identifying patients with sites-specific cancers diagnosis in HES-APE and NCRAS-CRD

Appendix 3. Procedure codes indicating breast and lung surgery in HES-APE

OPCS-4 coding system was used in HES-APE, the dictionary of OPCS-4.7, 4.8 and 4.9 published by NHS Digital Technology Reference Data Update Distribution (TRUD) was systematically searched to find out the surgery procedures in breast and lung.

Appendix 4. Product codes for identifying medication prescription in CPRD Gold and Aurum

To identify the medications for breast cancer in CPRD Gold and Aurum, the BNF Headers “BREAST CANCER” and “LUNG CANCER” was used to identify the substance name, and searched the product codes of approved substance in the dictionary of Product code in CPRD Gold and Aurum. (done by Yubo Wang)

Appendix 5. Codes for identifying patients with interested clinical events

Appendix 6. Code for identifying the treatment strategies in Cancer Registry

To identify treatment types in CPRD Cancer Registration Dictionary Set 17.

Appendix 7. Code for identifying the cause of mortality in the ONS death certificate

To identify treatment types in ONS death registration data: Data dictionary set 17 published by CPRD, in which the cause of death was classified by ICD coding system.

Appendix 16. Chapter 6: Medical code of breast cancer in CPRD Gold

Terms of disease	Medical code
Malignant neoplasm of female breast	3968
Ca female breast	348
Malignant neoplasm of nipple and areola of female breast	26853
Malignant neoplasm of nipple of female breast	23380
Malignant neoplasm of areola of female breast	64686
Malignant neoplasm of nipple or areola of female breast NOS	59831
Malignant neoplasm of central part of female breast	31546
Malignant neoplasm of upper-inner quadrant of female breast	29826
Malignant neoplasm of lower-inner quadrant of female breast	45222
Malignant neoplasm of upper-outer quadrant of female breast	23399
Malignant neoplasm of lower-outer quadrant of female breast	42070
Malignant neoplasm of axillary tail of female breast	20685
Malignant neoplasm, overlapping lesion of breast	49148
Malignant neoplasm of other site of female breast	56715
Malignant neoplasm of ectopic site of female breast	95057
Malignant neoplasm of other site of female breast NOS	38475
Malignant neoplasm of female breast NOS	9470
Malignant neoplasm of male breast	19423
Malignant neoplasm of nipple and areola of male breast	54494
Malignant neoplasm of nipple of male breast	68480
Malignant neoplasm of areola of male breast	67884
Malignant neoplasm of other site of male breast	54202
Malignant neoplasm of ectopic site of male breast	95323
Malignant neoplasm of male breast NOS	48809
Local recurrence of malignant tumour of breast	105488
[M]Infiltrating duct carcinoma	8351
[M]Intraductal papillary adenocarcinoma with invasion	30189
[M]Infiltrating duct and lobular carcinoma	39760
[M]Comedocarcinoma, noninfiltrating	62871
[M]Comedocarcinoma NOS	58131
[M]Juvenile breast carcinoma	40359
[M]Secretory breast carcinoma	67701
[M]Noninfiltrating intraductal papillary adenocarcinoma	102593
[M]Medullary carcinoma with lymphoid stroma	98883
[M]Lobular carcinoma NOS	12427
[M]Infiltrating ductular carcinoma	7319
[M]Inflammatory carcinoma	32472
[M]Paget's disease, mammary	12300
[M]Paget's disease, breast	60803
[M]Paget's disease and infiltrating breast duct carcinoma	42542
[M]Paget's disease and intraductal carcinoma of breast	12480
[M]Cystosarcoma phyllodes NOS	39312

[M]Cystosarcoma phyllodes, malignant	59251
[X]Malignant neoplasm of breast	12499

Appendix 17. Chapter 6: Medical code of breast cancer in CPRD Aurum

Terms of disease	Medical code
Local recurrence of malignant tumour of breast	1803781000006110
[RFC] Breast cancer	907341000006116
Malignant neoplasm of female breast	1210642019
Ca female breast	531851000006119
Ca breast - NOS	990571000006118
Carcinoma breast	880261000006119
Malignant neoplasm of nipple and areola of female breast	289137018
Ca breast - nipple/central	880271000006114
Malignant neoplasm of nipple of female breast	155417012
Malignant neoplasm of areola of female breast	155089014
Malignant neoplasm of nipple or areola of female breast NOS	289140018
Malignant neoplasm of central part of female breast	289141019
Malignant neoplasm of upper-inner quadrant of female breast	289142014
Ca breast-upper,inner quadrant	880281000006112
Malignant neoplasm of lower-inner quadrant of female breast	289143016
Ca breast-lower,inner quadrant	880291000006110
Malignant neoplasm of upper-outer quadrant of female breast	289144010
Ca breast-upper,outer quadrant	880301000006111
Malignant neoplasm of lower-outer quadrant of female breast	289145011
Ca breast-lower,outer quadrant	880311000006114
Malignant neoplasm of axillary tail of female breast	289146012
Ca breast - axillary tail	880321000006118
Malignant neoplasm, overlapping lesion of breast	289147015
Malignant neoplasm of other site of female breast	289148013
Malignant neoplasm of ectopic site of female breast	289149017
Malignant neoplasm of other site of female breast NOS	289150017
Malignant neoplasm of female breast NOS	289151018
Ca breast - NOS	880331000006115
Malignant neoplasm of male breast	155364013
Ca breast - male	880341000006113
Malignant neoplasm of nipple and areola of male breast	289153015
Malignant neoplasm of nipple of male breast	155418019

Terms of disease	Medical code
Malignant neoplasm of areola of male breast	155090017
Malignant neoplasm of nipple or areola of male breast NOS	289156011
Malignant neoplasm of other site of male breast	289157019
Malignant neoplasm of ectopic site of male breast	289158012
Malignant neoplasm of male breast NOS	289159016
Local recurrence of malignant tumour of breast	459378019
[M]Infiltrating duct carcinoma	310311000006110
[M]Intraductal papillary adenocarcinoma with invasion	1232564019
[M]Infiltrating duct and lobular carcinoma	1228259019
[M]Comedocarcinoma, noninfiltrating	307131000006115
[M]Comedocarcinoma NOS	291536017
[M]Juvenile breast carcinoma	310741000006110
[M]Secretory breast carcinoma	316311000006112
[M]Noninfiltrating intraductal papillary adenocarcinoma	314091000006113
[M]Noninfiltrating intracystic carcinoma	314081000006110
[M]Medullary carcinoma with lymphoid stroma	312171000006116
[M]Lobular carcinoma NOS	291540014
[M]Infiltrating ductular carcinoma	310321000006119
[M]Inflammatory carcinoma	310341000006114
[M]Paget's disease, mammary	314711000006117
[M]Paget's disease, breast	314691000006115
[M]Paget's disease and infiltrating breast duct carcinoma	314671000006116
[M]Paget's disease and intraductal carcinoma of breast	1231363012
[M]Cystosarcoma phyllodes NOS	291695012
[M]Cystosarcoma phyllodes, malignant	307441000006115
[X]Malignant neoplasm of breast	292137017

Appendix 18. Chapter 6: ICD-10 codes of breast cancer in Cancer Registry

Disease term	ICD-10 codes
Malignant neoplasm of breast	C50
Malignant neoplasm: Nipple and areola	C50.0
Malignant neoplasm: Central portion of breast	C50.1
Malignant neoplasm: Upper-inner quadrant of breast	C50.2
Malignant neoplasm: Lower-inner quadrant of breast	C50.3
Malignant neoplasm: Upper-outer quadrant of breast	C50.4
Malignant neoplasm: Lower-outer quadrant of breast	C50.5
Malignant neoplasm: Axillary tail of breast	C50.6
Malignant neoplasm: Overlapping lesion of breast	C50.8
Malignant neoplasm: Breast, unspecified	C50.9

Appendix 19. Chapter 6: Breast cancer-related medication

Type	Code	Description	BNF Code
Drug	Tamoxifen	Anti-oestrogens	0803041S0
	Anastrozole	Aromatase inhibitors	0803041B0
	Letrozole	Aromatase inhibitors	0803041L0
	Exemestane	Aromatase inhibitors	0803041C0

Appendix 20. Chapter 6: OPCS-4 codes for breast cancer and related operation

Strategy	OPCS	Term
Surgery	B271	Total mastectomy and excision of both pectoral muscles and part of the chest wall
	B272	Radical mastectomy/total mastectomy and excision of both pectoral muscles NEC.
	B273	Total mastectomy and excision of pectoralis minor muscle
	B274	Total mastectomy NEC, inc toilet and simple mastectomy, extended simple mastectomy.
	B275	Subcutaneous mastectomy
	B276	Skin sparing mastectomy
	B278	Total excision of breast other specified.
	B279	Unspecified, Mastectomy NEC.
	B281	Quadrantectomy of breast
	B282	Partial excision of breast, Partial mastectomy, WLE, includes wedge or segmental excision of breast NEC.
	B283	Excision of lesion of the breast, includes lumpectomy, excision biopsy.
	B284	Re-excision of breast margins
	B285	Wire guided partial excision of breast
	B286	Excision of accessory breast tissue
	B288	Other specified other excision of breast
	B289	Unspecified other excision of breast
	B341	Subareolar excision of mammillary duct
	B342	Excision of mammillary duct NEC
	B343	Excision of lesion of mammillary duct nec. Microdochectomy.
	B352	Excision of nipple
	B353	Extirpation/removal of lesion of nipple.
	B374	Capsulectomy of breast
	B401	Interstitial laser destruction of lesion of breast
	B408	Destruction of lesion of breast, Other specified
	B409	Destruction of lesion of breast, Unspecified

Appendix 21. Chapter 6: Read terms for Charlson Comorbidity Index

Read/OXMIS term	Disease category	Charlson score weight
HIV disease resulting in unspecified malignant neoplasm	AIDS	6
HIV disease resulting in multiple diseases CE	AIDS	6
[X]Human immunodeficiency virus disease	AIDS	6
HIV disease resulting in mycobacterial infection	AIDS	6
Human immunodeficiency virus with neurological disease	AIDS	6
[X]HIV disease resulting in other non-Hodgkin's lymphoma	AIDS	6
HIV disease resulting/unspcf infectious disease	AIDS	6
Acquired human immunodeficiency virus infection syndrome NOS	AIDS	6
[X]HIV disease resulting in unspecified malignant neoplasm	AIDS	6
[X]HIV disease resulting in multiple infections	AIDS	6
HIV disease resulting in candidiasis	AIDS	6
Human immunodeficiency virus with secondary infection	AIDS	6
[X]HIV disease resulting in other bacterial infections	AIDS	6
[X]Unspecified human immunodeficiency virus [HIV] disease	AIDS	6
[X]HIV disease resulting in other specified conditions	AIDS	6
HIV disease resulting in Burkitt's lymphoma	AIDS	6
[X]HIV disease resulting in other mycoses	AIDS	6
HIV disease resulting in lymphoid interstitial pneumonitis	AIDS	6
Human immunodef virus resulting in other disease	AIDS	6
HIV disease resulting in wasting syndrome	AIDS	6
[X]HIV disease resulting in other viral infections	AIDS	6
Human immunodeficiency virus with constitutional disease	AIDS	6
Acquired immune deficiency syndrome	AIDS	6
[X]HIV disease result/haematological???? abnorms,NEC	AIDS	6
AIDS	AIDS	6
HIV disease resulting in cytomegaloviral disease	AIDS	6
HIV disease resulting in Kaposi's sarcoma	AIDS	6
HIV infection with persistent generalised lymphadenopathy	AIDS	6
HIV disease result/haematological???? abnorms,NEC	AIDS	6
Human immunodeficiency virus with other clinical findings	AIDS	6
Human immunodeficiency virus with secondary cancers	AIDS	6
ACQUIRED IMMUNE DEFICIENCY SYNDROME	AIDS	6
HIV disease resulting in Pneumocystis carinii pneumonia	AIDS	6

Read/OXMIS term	Disease category	Charlson score weight
[X]HIV disease resulting/unspcf infectious??? disease	AIDS	6
HIV dis reslt/oth mal neopl/lymph,h'matopoetc? tissu	AIDS	6
[X]HIV dis reslt/oth mal neopl/lymph,h'matopoetc? tissu	AIDS	6
Asymptomatic human immunodeficiency virus infection	AIDS	6
[X]HIV disease resulting in other malignant neoplasms	AIDS	6
[X]HIV disease resulting/other infectious??? diseases	AIDS	6
HIV disease resulting in multiple infections	AIDS	6
HIV disease resulting in multiple malignant neoplasms	AIDS	6
[X]HIV disease resulting in multiple diseases CE	AIDS	6
Cerebrovascular disease NOS	Cerebrovascular disease	1
Intracranial haemorrhage NOS	Cerebrovascular disease	1
Cerebellar haemorrhage	Cerebrovascular disease	1
Cerebrovascular disease	Cerebrovascular disease	1
Other cerebrovascular disease	Cerebrovascular disease	1
Right sided intracerebral haemorrhage, unspecified	Cerebrovascular disease	1
MENINGEAL HAEMORRHAGE TRAUMATIC	Cerebrovascular disease	1
Precerebral artery occlusion NOS	Cerebrovascular disease	1
Subarachnoid haemorrh from intracranial artery, unspecif	Cerebrovascular disease	1
Subarachnoid haemorrhage from vertebral artery	Cerebrovascular disease	1
Traumatic subdural haemorrhage	Cerebrovascular disease	1
CEREBROVASCULAR DISEASE WITH HYPERTENSIO	Cerebrovascular disease	1
Transient cerebral ischaemia NOS	Cerebrovascular disease	1
Stenosis of precerebral arteries	Cerebrovascular disease	1
Evacuation of intracerebral haematoma NEC	Cerebrovascular disease	1
Other cerebrovascular disease OS	Cerebrovascular disease	1
HAEMORRHAGE INTRACEREBRAL	Cerebrovascular disease	1
[X]Occlusion and stenosis of other cerebral arteries	Cerebrovascular disease	1
Sequelae/other unspecified cerebrovascular diseases	Cerebrovascular disease	1
MENINGEAL HAEMORRHAGE	Cerebrovascular disease	1

Read/OXMIS term	Disease category	Charlson score weight
Precerebral arterial occlusion	Cerebrovascular disease	1
Transient cerebral ischaemia NOS	Cerebrovascular disease	1
Intracerebral haemorrhage NOS	Cerebrovascular disease	1
Generalised ischaemic cerebrovascular disease NOS	Cerebrovascular disease	1
CEREBROVASCULAR DISEASE	Cerebrovascular disease	1
Other transient cerebral ischaemia	Cerebrovascular disease	1
Cerebral degeneration due to cerebrovascular disease	Cerebrovascular disease	1
Occlusion??? of multiple and bilat cerebral arteries	Cerebrovascular disease	1
Subarachnoid haemorrhage	Cerebrovascular disease	1
[X]Cerebrovascular diseases	Cerebrovascular disease	1
HAEMORRHAGE INTRACEREBRAL WITH HYPERTENS	Cerebrovascular disease	1
CVA - cerebrovascular accid due to intracerebral haemorrhage	Cerebrovascular disease	1
Other precerebral artery occlusion	Cerebrovascular disease	1
Subdural haemorrhage NOS	Cerebrovascular disease	1
Open traumatic subarachnoid haemorrhage	Cerebrovascular disease	1
Other specified cerebrovascular disease	Cerebrovascular disease	1
Transient cerebral ischaemia	Cerebrovascular disease	1
[X]Other specified cerebrovascular diseases	Cerebrovascular disease	1
Intracerebral haemorrhage, multiple localized	Cerebrovascular disease	1
[X]Occlusion and stenosis of other precerebral arteries	Cerebrovascular disease	1
H/O: cerebrovascular disease	Cerebrovascular disease	1
[X]Sequelae/other unspecified cerebrovascular diseases	Cerebrovascular disease	1
Subarachnoid haemorrhage from anterior communicating artery	Cerebrovascular disease	1
Subarachnoid haemorrhage from posterior communicating artery	Cerebrovascular disease	1
Sequelae of intracerebral haemorrhage	Cerebrovascular disease	1
[X]Other intracerebral haemorrhage	Cerebrovascular disease	1
Subarachnoid haemorrhage from middle cerebral artery	Cerebrovascular disease	1
Other cerebrovascular disease NOS	Cerebrovascular disease	1

Read/OXMIS term	Disease category	Charlson score weight
Left sided intracerebral haemorrhage, unspecified	Cerebrovascular disease	1
Intracerebral haemorrhage in hemisphere, unspecified	Cerebrovascular disease	1
Generalised ischaemic cerebrovascular disease NOS	Cerebrovascular disease	1
Cerebral infarction due to embolism of cerebral arteries	Cerebrovascular disease	1
[X]Intracerebral haemorrhage in hemisphere, unspecified	Cerebrovascular disease	1
Intracerebral haemorrhage, intraventricular	Cerebrovascular disease	1
Sequelae of subarachnoid haemorrhage	Cerebrovascular disease	1
HAEMORRHAGE INTRACRANIAL	Cerebrovascular disease	1
Traumatic subarachnoid haemorrhage	Cerebrovascular disease	1
Subarachnoid haemorrhage NOS	Cerebrovascular disease	1
HAEMORRHAGE SUBARACHNOID TRAUMATIC	Cerebrovascular disease	1
TRANSIENT CEREBRAL ISCHAEMIA WITH HYPERT	Cerebrovascular disease	1
Subarachnoid haemorrhage following injury	Cerebrovascular disease	1
Multiple and bilateral precerebral arterial occlusion	Cerebrovascular disease	1
Stroke due to intracerebral haemorrhage	Cerebrovascular disease	1
Ruptured berry aneurysm	Cerebrovascular disease	1
Subarachnoid haemorrhage from carotid siphon and bifurcation	Cerebrovascular disease	1
Intracerebral haemorrhage	Cerebrovascular disease	1
Subarachnoid haemorrhage from basilar artery	Cerebrovascular disease	1
Late effects of cerebrovascular disease	Cerebrovascular disease	1
[X]Other subarachnoid haemorrhage	Cerebrovascular disease	1
Closed traumatic subarachnoid haemorrhage	Cerebrovascular disease	1
SUBARACHNOID HAEMORRHAGE WITH HYPERTENSI	Cerebrovascular disease	1
[X]Subarachnoid haemorrhage from other intracranial arteries	Cerebrovascular disease	1
SUBARACHNOID HAEMORRHAGE	Cerebrovascular disease	1
CVA unspecified	Cerebrovascular disease	1
Middle cerebral artery syndrome	Cerebrovascular disease	1
Stroke monitoring	Cerebrovascular disease	1

Read/OXMIS term	Disease category	Charlson score weight
Cerebral palsy, not congenital or infantile, acute	Cerebrovascular disease	1
Anterior cerebral artery syndrome	Cerebrovascular disease	1
Stroke and cerebrovascular accident unspecified	Cerebrovascular disease	1
Left sided CVA	Cerebrovascular disease	1
CVA - Cerebrovascular accident unspecified	Cerebrovascular disease	1
Pure sensory lacunar syndrome	Cerebrovascular disease	1
Brain stem stroke syndrome	Cerebrovascular disease	1
Cerebellar stroke syndrome	Cerebrovascular disease	1
Pure motor lacunar syndrome	Cerebrovascular disease	1
Right sided CVA	Cerebrovascular disease	1
Stroke unspecified	Cerebrovascular disease	1
H/O: CVA/stroke	Cerebrovascular disease	1
Posterior cerebral artery syndrome	Cerebrovascular disease	1
H/O: stroke	Cerebrovascular disease	1
Stroke due to cerebral arterial occlusion	Cerebrovascular disease	1
STROKE	Cerebrovascular disease	1
[X]Hypersensitivity pneumonitis due to other organic dusts	Chronic pulmonary disease	1
Pituitary snuff-takers' disease	Chronic pulmonary disease	1
Flax-dressers' disease	Chronic pulmonary disease	1
Severe asthma attack	Chronic pulmonary disease	1
Allergic alveolitis and pneumonitis NOS	Chronic pulmonary disease	1
Panlobular emphysema	Chronic pulmonary disease	1
BIRD FANCIER'S LUNG	Chronic pulmonary disease	1
ASTHMA ATTACK	Chronic pulmonary disease	1
Sequoiosis (red-cedar asthma)	Chronic pulmonary disease	1
Mild asthma	Chronic pulmonary disease	1
Malt workers' lung	Chronic pulmonary disease	1
Budgerigar-fanciers' lung	Chronic pulmonary disease	1

Read/OXMIS term	Disease category	Charlson score weight
Other emphysema	Chronic pulmonary disease	1
Talc pneumoconiosis	Chronic pulmonary disease	1
NOCTURNAL ASTHMA	Chronic pulmonary disease	1
Asthma	Chronic pulmonary disease	1
Bird-fancier's lung	Chronic pulmonary disease	1
Simple chronic bronchitis	Chronic pulmonary disease	1
Bagassosis	Chronic pulmonary disease	1
Pollen asthma	Chronic pulmonary disease	1
ASTHMA ALLERGIC GRASS	Chronic pulmonary disease	1
EXCISION BRONCHIECTASIS	Chronic pulmonary disease	1
Chest infection - unspecified bronchitis	Chronic pulmonary disease	1
Obstructive chronic bronchitis	Chronic pulmonary disease	1
Severe asthma	Chronic pulmonary disease	1
Post-infective bronchiectasis	Chronic pulmonary disease	1
ASTHMA	Chronic pulmonary disease	1
Asthma causes daytime symptoms most days	Chronic pulmonary disease	1
ASTHMA EPISODIC	Chronic pulmonary disease	1
Other chronic bronchitis NOS	Chronic pulmonary disease	1
Occasional asthma	Chronic pulmonary disease	1
BYSSINOSIS	Chronic pulmonary disease	1
Wood asthma	Chronic pulmonary disease	1
Moderate asthma	Chronic pulmonary disease	1
Bronchiectasis NOS	Chronic pulmonary disease	1
Asthma never causes daytime symptoms	Chronic pulmonary disease	1
EMPHYSEMA PULMONARY	Chronic pulmonary disease	1
Mixed asthma	Chronic pulmonary disease	1
Asthma disturbs sleep weekly	Chronic pulmonary disease	1
FARMERS' LUNG	Chronic pulmonary disease	1

Read/OXMIS term	Disease category	Charlson score weight
Mushroom workers' lung	Chronic pulmonary disease	1
Simple chronic bronchitis NOS	Chronic pulmonary disease	1
Exercise induced asthma	Chronic pulmonary disease	1
ASTHMA ACUTE	Chronic pulmonary disease	1
Asbestosis NOS	Chronic pulmonary disease	1
TRACHEOBRONCHITIS	Chronic pulmonary disease	1
Asthma causing night waking	Chronic pulmonary disease	1
Asthma restricts exercise	Chronic pulmonary disease	1
Silica pneumoconiosis NOS	Chronic pulmonary disease	1
Chronic pulmonary fibrosis due to chemical fumes	Chronic pulmonary disease	1
Asthma - currently dormant	Chronic pulmonary disease	1
Asthma causes daytime symptoms 1 to 2 times per month	Chronic pulmonary disease	1
Hay fever with asthma	Chronic pulmonary disease	1
Extrinsic allergic alveolitis	Chronic pulmonary disease	1
Asthma monitored	Chronic pulmonary disease	1
Status asthmaticus NOS	Chronic pulmonary disease	1
Chronic obstructive pulmonary disease NOS	Chronic pulmonary disease	1
Asthma unspecified	Chronic pulmonary disease	1
Atrophic (senile) emphysema	Chronic pulmonary disease	1
CHRONIC ASTHMA	Chronic pulmonary disease	1
ASTHMA EXACERBATION	Chronic pulmonary disease	1
Chronic bullous emphysema	Chronic pulmonary disease	1
CHRONIC BRONCHITIS WITH EMPHYSEMA	Chronic pulmonary disease	1
Centrilobular emphysema	Chronic pulmonary disease	1
Allergic alveolitis and pneumonitis NOS	Chronic pulmonary disease	1
CHRONIC SPASMODIC BRONCHITIS	Chronic pulmonary disease	1
ASTHMA FREQUENCY REGULARLY	Chronic pulmonary disease	1
ASTHMA POLLEN INITIATED	Chronic pulmonary disease	1

Read/OXMIS term	Disease category	Charlson score weight
Asthma sometimes restricts exercise	Chronic pulmonary disease	1
Suberosis (cork-handlers' lung)	Chronic pulmonary disease	1
Childhood asthma	Chronic pulmonary disease	1
Asthma night-time symptoms	Chronic pulmonary disease	1
Other emphysema NOS	Chronic pulmonary disease	1
Asthma never restricts exercise	Chronic pulmonary disease	1
Silica and silicate pneumoconiosis	Chronic pulmonary disease	1
ASTHMA SEVERITY MILD	Chronic pulmonary disease	1
Bronchitis and pneumonitis due to chemical fumes	Chronic pulmonary disease	1
EXACERBATION OF ASTHMA	Chronic pulmonary disease	1
INTRINSIC ASTHMA	Chronic pulmonary disease	1
ANTHRACOSILICOSIS	Chronic pulmonary disease	1
Obstructive chronic bronchitis NOS	Chronic pulmonary disease	1
MacLeod's unilateral emphysema	Chronic pulmonary disease	1
ASTHMA AND BRONCHITIS	Chronic pulmonary disease	1
ASTHMA FREQUENCY ON EXERCISE ONLY	Chronic pulmonary disease	1
Occupational asthma	Chronic pulmonary disease	1
Other chronic bronchitis	Chronic pulmonary disease	1
Allergic bronchitis NEC	Chronic pulmonary disease	1
PIGEON FANCIER'S LUNG	Chronic pulmonary disease	1
Pneumoconiosis due to inorganic dust NOS	Chronic pulmonary disease	1
Extrinsic asthma with asthma attack	Chronic pulmonary disease	1
Bronchitis unspecified	Chronic pulmonary disease	1
Lung disease due to external agents NOS	Chronic pulmonary disease	1
Asbestosis	Chronic pulmonary disease	1
Attends asthma monitoring	Chronic pulmonary disease	1
Pigeon-fanciers' lung	Chronic pulmonary disease	1
Intrinsic asthma	Chronic pulmonary disease	1

Read/OXMIS term	Disease category	Charlson score weight
Late onset asthma	Chronic pulmonary disease	1
C/O bronchial catarrh	Chronic pulmonary disease	1
Chronic bronchitis	Chronic pulmonary disease	1
BRONCHITIS ACUTE ON CHRONIC	Chronic pulmonary disease	1
Farmers' lung	Chronic pulmonary disease	1
BRONCHITIS PURULENT	Chronic pulmonary disease	1
Brittle asthma	Chronic pulmonary disease	1
Compensatory emphysema	Chronic pulmonary disease	1
Lung disease with diseases EC NOS	Chronic pulmonary disease	1
BRONCHITIS RECURRENT	Chronic pulmonary disease	1
Mucopurulent chronic bronchitis	Chronic pulmonary disease	1
Chronic tracheobronchitis	Chronic pulmonary disease	1
Giant bullous emphysema	Chronic pulmonary disease	1
Asthma disturbing sleep	Chronic pulmonary disease	1
Smokers' cough	Chronic pulmonary disease	1
Chronic pulmonary fibrosis following radiation	Chronic pulmonary disease	1
Asthma confirmed	Chronic pulmonary disease	1
Chronic emphysema due to chemical fumes	Chronic pulmonary disease	1
Intrinsic asthma without status asthmaticus	Chronic pulmonary disease	1
Late-onset asthma	Chronic pulmonary disease	1
Recurrent bronchiectasis	Chronic pulmonary disease	1
Pleural plaque disease due to asbestosis	Chronic pulmonary disease	1
Acute exacerbation of asthma	Chronic pulmonary disease	1
BRONCHITIS ALLERGIC CHRONIC	Chronic pulmonary disease	1
BRONCHIAL ASTHMA	Chronic pulmonary disease	1
Emergency admission, asthma	Chronic pulmonary disease	1
Coal workers' pneumoconiosis	Chronic pulmonary disease	1
ASTHMA HIGH RISK	Chronic pulmonary disease	1

Read/OXMIS term	Disease category	Charlson score weight
ECZEMA WITH ASTHMA	Chronic pulmonary disease	1
ASTHMA EXERCISE INDUCED	Chronic pulmonary disease	1
H/O: asthma	Chronic pulmonary disease	1
Chronic bullous emphysema NOS	Chronic pulmonary disease	1
Chronic catarrhal bronchitis	Chronic pulmonary disease	1
Mixed simple and mucopurulent chronic bronchitis	Chronic pulmonary disease	1
Chronic bronchitis NOS	Chronic pulmonary disease	1
Intrinsic asthma NOS	Chronic pulmonary disease	1
Siderosis	Chronic pulmonary disease	1
Bronchiectasis	Chronic pulmonary disease	1
Emphysematous bronchitis	Chronic pulmonary disease	1
Bird-fancier's lung NOS	Chronic pulmonary disease	1
Intrinsic asthma with status asthmaticus	Chronic pulmonary disease	1
Other allergic alveolitis NOS	Chronic pulmonary disease	1
Stannosis	Chronic pulmonary disease	1
Asthma attack NOS	Chronic pulmonary disease	1
Furriers' lung	Chronic pulmonary disease	1
BRONCHITIS SUBACUTE	Chronic pulmonary disease	1
Asthma attack	Chronic pulmonary disease	1
Asthma causes night symptoms 1 to 2 times per month	Chronic pulmonary disease	1
Emphysema NOS	Chronic pulmonary disease	1
Extrinsic asthma NOS	Chronic pulmonary disease	1
Bronchial asthma	Chronic pulmonary disease	1
Acute vesicular emphysema	Chronic pulmonary disease	1
Asthma daytime symptoms	Chronic pulmonary disease	1
Obliterative bronchiolitis due to chemical fumes	Chronic pulmonary disease	1
[X]Pneumoconiosis due to other dust containing silica	Chronic pulmonary disease	1
STATUS ASTHMATICUS	Chronic pulmonary disease	1

Read/OXMIS term	Disease category	Charlson score weight
Hay fever with asthma	Chronic pulmonary disease	1
Pneumoconiosis due to other inorganic dust	Chronic pulmonary disease	1
ASTHMA EXERCISE INCLUDED	Chronic pulmonary disease	1
ASTHMA SEVERITY MODERATE	Chronic pulmonary disease	1
Massive silicotic fibrosis	Chronic pulmonary disease	1
BRONCHIECTASIS	Chronic pulmonary disease	1
Bronchitis and pneumonitis due to chemical fumes NOS	Chronic pulmonary disease	1
Extrinsic asthma without status asthmaticus	Chronic pulmonary disease	1
CHRONIC BRONCHITIS	Chronic pulmonary disease	1
Hypersensitivity pneumonitis NOS	Chronic pulmonary disease	1
BRONCHITIS OBSTRUCTIVE	Chronic pulmonary disease	1
Asthma causes daytime symptoms 1 to 2 times per week	Chronic pulmonary disease	1
ASTHMA OCCASIONAL	Chronic pulmonary disease	1
Asthma limiting activities	Chronic pulmonary disease	1
Lung disease with diseases EC	Chronic pulmonary disease	1
OBSTRUCTIVE LUNG DISEASE COMPENSATORY	Chronic pulmonary disease	1
Purulent chronic bronchitis	Chronic pulmonary disease	1
Interstitial emphysema	Chronic pulmonary disease	1
OBSTRUCTIVE LUNG DISEASE	Chronic pulmonary disease	1
Pneumoconiosis NOS	Chronic pulmonary disease	1
Mucopurulent chronic bronchitis NOS	Chronic pulmonary disease	1
Subcutaneous emphysema	Chronic pulmonary disease	1
WHEEZING BRONCHIAL	Chronic pulmonary disease	1
[X]Pneumoconiosis due to other specified inorganic dusts	Chronic pulmonary disease	1
Tracheobronchitis NOS	Chronic pulmonary disease	1
Asthma limits walking up hills or stairs	Chronic pulmonary disease	1
Byssinosis	Chronic pulmonary disease	1
Maple bark strippers' lung	Chronic pulmonary disease	1

Read/OXMIS term	Disease category	Charlson score weight
Bronchitis NOS	Chronic pulmonary disease	1
Asthma treatment compliance unsatisfactory	Chronic pulmonary disease	1
Aspirin induced asthma	Chronic pulmonary disease	1
Absent from work or school due to asthma	Chronic pulmonary disease	1
Berylliosis	Chronic pulmonary disease	1
Emphysema	Chronic pulmonary disease	1
Chronic asthmatic bronchitis	Chronic pulmonary disease	1
Asthma prophylactic medication used	Chronic pulmonary disease	1
BRONCHITIS	Chronic pulmonary disease	1
Segmental bullous emphysema	Chronic pulmonary disease	1
Asthma severely restricts exercise	Chronic pulmonary disease	1
Chronic wheezy bronchitis	Chronic pulmonary disease	1
Cannabinosis	Chronic pulmonary disease	1
Fetid chronic bronchitis	Chronic pulmonary disease	1
Allergic asthma NEC	Chronic pulmonary disease	1
LATE ONSET ASTHMA	Chronic pulmonary disease	1
BRONCHITIS ALLERGIC	Chronic pulmonary disease	1
Aluminosis of lung	Chronic pulmonary disease	1
ASBESTOSIS	Chronic pulmonary disease	1
Intrinsic asthma with asthma attack	Chronic pulmonary disease	1
Bauxite fibrosis of lung	Chronic pulmonary disease	1
[X]Other emphysema	Chronic pulmonary disease	1
Detergent asthma	Chronic pulmonary disease	1
Other allergic alveolitis	Chronic pulmonary disease	1
Extrinsic (atopic) asthma	Chronic pulmonary disease	1
Exercise induced asthma	Chronic pulmonary disease	1
CARDIAC ASTHMA	Congestive heart disease	1
Cardiac failure NOS	Congestive heart disease	1

Read/OXMIS term	Disease category	Charlson score weight
Decompensated cardiac failure	Congestive heart disease	1
Hypertensive heart&renal dis wth (congestive) heart failure	Congestive heart disease	1
HEART FAILURE LEFT-SIDED	Congestive heart disease	1
LVF (LEFT VENTRICULAR FAILURE)	Congestive heart disease	1
Weak heart	Congestive heart disease	1
Heart failure annual review	Congestive heart disease	1
MYOCARDIAL FAILURE	Congestive heart disease	1
Congestive cardiomyopathy	Congestive heart disease	1
Compensated cardiac failure	Congestive heart disease	1
Right heart failure	Congestive heart disease	1
Cardiac failure therapy	Congestive heart disease	1
CONGESTIVE CARDIAC FAILURE	Congestive heart disease	1
Congestive cardiac failure	Congestive heart disease	1
Acute heart failure	Congestive heart disease	1
H/O: Heart failure in last year	Congestive heart disease	1
Acute left ventricular failure	Congestive heart disease	1
Heart failure as a complication of care	Congestive heart disease	1
Chronic congestive heart failure	Congestive heart disease	1
Heart failure care plan discussed with patient	Congestive heart disease	1
CONGESTIVE CARDIOMYOPATHY	Congestive heart disease	1
LEFT VENTRICULAR FAILURE ACUTE	Congestive heart disease	1
Left ventricular failure	Congestive heart disease	1
CONGESTIVE HEART FAILURE	Congestive heart disease	1
Heart failure	Congestive heart disease	1
HEART FAILURE ACUTE	Congestive heart disease	1
Congestive heart failure	Congestive heart disease	1
H/O: heart failure	Congestive heart disease	1
WEAK HEART	Congestive heart disease	1

Read/OXMIS term	Disease category	Charlson score weight
Cardiac failure	Congestive heart disease	1
Heart failure confirmed	Congestive heart disease	1
HYPERTENSION CONGESTIVE HEART FAILURE	Congestive heart disease	1
Acute congestive heart failure	Congestive heart disease	1
HEART FAILURE RIGHT-SIDED	Congestive heart disease	1
Admit heart failure emergency	Congestive heart disease	1
CONGESTIVE HEART FAILURE COMPENSATED	Congestive heart disease	1
Heart failure NOS	Congestive heart disease	1
CONGESTIVE HEART FAILURE DECOMPENSATED	Congestive heart disease	1
HEART FAILURE	Congestive heart disease	1
DEMENTIA	Dementia	1
Presenile dementia NOS	Dementia	1
Arteriosclerotic dementia with paranoia	Dementia	1
[X]Alzheimer's dementia unspec	Dementia	1
Uncomplicated presenile dementia	Dementia	1
DEMENTIA ARTERIOSCLEROTIC	Dementia	1
[X]Vascular dementia, unspecified	Dementia	1
[X]Lewy body dementia	Dementia	1
[X]Senile dementia,Alzheimer's type	Dementia	1
Multi infarct dementia	Dementia	1
[X] Senile dementia NOS	Dementia	1
Dementia in conditions EC	Dementia	1
[X]Predominantly cortical dementia	Dementia	1
[X] Senile dementia, depressed or paranoid type	Dementia	1
[X]Dementia in Alzheimer's disease	Dementia	1
SENILE DETERIORATION	Dementia	1
[X] Unspecified dementia	Dementia	1
[X]Presenile dementia,Alzheimer's type	Dementia	1
Arteriosclerotic dementia	Dementia	1
[X]Dementia in other diseases classified elsewhere	Dementia	1
[X]Vascular dementia of acute onset	Dementia	1
[X]Multi-infarct dementia	Dementia	1
DEMENTIA AGGRESSIVE	Dementia	1
Uncomplicated senile dementia	Dementia	1
Arteriosclerotic dementia NOS	Dementia	1
[X]Dementia in other specified diseases classif elsewhere	Dementia	1
Presenile dementia	Dementia	1
[X]Dementia in Alzheimer's disease, unspecified	Dementia	1

Read/OXMIS term	Disease category	Charlson score weight
[X]Other vascular dementia	Dementia	1
[X]Arteriosclerotic dementia	Dementia	1
[X]Primary degen dementia of Alzheimer's type, senile onset	Dementia	1
Uncomplicated arteriosclerotic dementia	Dementia	1
Senile/presenile dementia	Dementia	1
[X]Dementia in Alzheimer's dis, atypical or mixed type	Dementia	1
Senile dementia	Dementia	1
Arteriosclerotic dementia with depression	Dementia	1
Arteriosclerotic dementia with delirium	Dementia	1
SENILE DEMENTIA	Dementia	1
[X]Dementia in Alzheimer's disease with late onset	Dementia	1
[X]Vascular dementia	Dementia	1
PRESENILE DEMENTIA	Dementia	1
[X] Primary degenerative dementia NOS	Dementia	1
H/O: dementia	Dementia	1
[X]Subcortical vascular dementia	Dementia	1
Uncomplicated senile dementia	Dementia	1
[X]Primary degen dementia, Alzheimer's type, presenile onset	Dementia	1
[X]Dementia in Alzheimer's disease with early onset	Dementia	1
[X]Mixed cortical and subcortical vascular dementia	Dementia	1
Unstable diabetes	Diabetes	1
Insulin dependent diabetes mellitus with gangrene	Diabetes	1
Diabetes mellitus, adult onset, with ketoacidosis	Diabetes	1
Lipoatrophic diabetes mellitus	Diabetes	1
Diabetes mellitus, juvenile type, with ketoacidotic coma	Diabetes	1
Non-insulin dependent diabetes mellitus with gangrene	Diabetes	1
Non-insulin-dependent diabetes mellitus without complication	Diabetes	1
Type 2 diabetes mellitus with ulcer	Diabetes	1
Type 2 diabetes mellitus with arthropathy	Diabetes	1
NIDDM - Non-insulin dependent diabetes mellitus	Diabetes	1
Type II diabetes mellitus with arthropathy	Diabetes	1
Diabetes mellitus with unspecified complication	Diabetes	1
Type I diabetes mellitus with ketoacidosis	Diabetes	1
Diabetes mellitus, adult with gangrene	Diabetes	1
GANGRENE DIABETIC	Diabetes	1
Insulin treated Type 2 diabetes mellitus	Diabetes	1
Type I diabetes mellitus maturity onset	Diabetes	1
Diabetes mellitus NOS with hyperosmolar coma	Diabetes	1
HYPOGLYCAEMIC COMA DIABETIC	Diabetes	1
MATURITY ONSET DIABETES MELLITUS INSULIN	Diabetes	1

Read/OXMIS term	Disease category	Charlson score weight
Diabetic peripheral angiopathy	Diabetes	1
HYPOGLYCAEMIA IN DIABETES MELLITUS	Diabetes	1
Diabetic - poor control	Diabetes	1
Insulin treated Type II diabetes mellitus	Diabetes	1
Type 2 diabetes mellitus with peripheral angiopathy	Diabetes	1
Non-insulin-dependent diabetes mellitus with multiple comps	Diabetes	1
Unstable insulin dependent diabetes mellitus	Diabetes	1
Type 2 diabetes mellitus without complication	Diabetes	1
Diabetes mellitus with other specified manifestation	Diabetes	1
Type II diabetes mellitus	Diabetes	1
Type 2 diabetes mellitus with persistent proteinuria	Diabetes	1
UNSTABLE DIABETIC	Diabetes	1
Non-insulin dependent diabetes mellitus with arthropathy	Diabetes	1
Type 2 diabetes mellitus with arthropathy	Diabetes	1
Diabetic on insulin	Diabetes	1
Type II diabetes mellitus with gangrene	Diabetes	1
Pre-existing diabetes mellitus, non-insulin-dependent	Diabetes	1
PRURITUS DIABETIC	Diabetes	1
Type 2 diabetes mellitus with ketoacidosis	Diabetes	1
Unstable type 1 diabetes mellitus	Diabetes	1
Other specified diabetes mellitus with unspecified comps	Diabetes	1
Diabetes mellitus autosomal dominant type 2	Diabetes	1
Diabetes mellitus NOS with peripheral circulatory disorder	Diabetes	1
Type 1 diabetes mellitus with ketoacidotic coma	Diabetes	1
DIABETIC CATARACT	Diabetes	1
Diabetes mellitus, juvenile type, with ketoacidosis	Diabetes	1
Insulin dependent diabetes mellitus	Diabetes	1
DIABETIC ACIDOSIS	Diabetes	1
Unstable type I diabetes mellitus	Diabetes	1
SUGAR DIABETES	Diabetes	1
Diabetes mellitus with ketoacidotic coma	Diabetes	1
Diabetes mellitus with gangrene	Diabetes	1
KETOSIS DIABETIC	Diabetes	1
DIABETES	Diabetes	1
Type 1 diabetes mellitus with ulcer	Diabetes	1
Non-insulin dependent diabetes mellitus with ulcer	Diabetes	1
Other specified diabetes mellitus with other spec comps	Diabetes	1
ABSCESS DIABETIC	Diabetes	1
Type II diabetes mellitus - poor control	Diabetes	1
Malnutrition-related diabetes mellitus with coma	Diabetes	1

Read/OXMIS term	Disease category	Charlson score weight
Type 2 diabetes mellitus	Diabetes	1
Insulin treated non-insulin dependent diabetes mellitus	Diabetes	1
Diabetic stabilisation	Diabetes	1
Insulin dependent diabetes mellitus	Diabetes	1
Type 1 diabetes mellitus with peripheral angiopathy	Diabetes	1
Type 1 diabetes mellitus with hypoglycaemic coma	Diabetes	1
Type I diabetes mellitus	Diabetes	1
Diabetes mellitus, adult, peripheral circulatory disorder	Diabetes	1
Malnutrition-related diabetes mellitus with ketoacidosis	Diabetes	1
Diabetes mellitus, juvenile type, with hyperosmolar coma	Diabetes	1
DIABETIC AMYOTROPHY	Diabetes	1
Type II diabetes mellitus with ulcer	Diabetes	1
Type 2 diabetes mellitus with gangrene	Diabetes	1
KETOACIDOSIS DIABETIC	Diabetes	1
Diabetes mellitus, adult onset, with hyperosmolar coma	Diabetes	1
Type I diabetes mellitus with hypoglycaemic coma	Diabetes	1
Hyperosmolar non-ketotic state in type 2 diabetes mellitus	Diabetes	1
ULCER DIABETIC	Diabetes	1
Diabetic - poor control NOS	Diabetes	1
Insulin treated Type II diabetes mellitus	Diabetes	1
Insulin dependent diabetes mellitus with ulcer	Diabetes	1
Insulin treated Type 2 diabetes mellitus	Diabetes	1
Type 1 diabetes mellitus - poor control	Diabetes	1
Type 1 diabetes mellitus - poor control	Diabetes	1
NIDDM with peripheral circulatory disorder	Diabetes	1
Secondary pancreatic diabetes mellitus	Diabetes	1
Type 1 diabetes mellitus with ketoacidosis	Diabetes	1
Diabetic on insulin and oral treatment	Diabetes	1
Pre-existing diabetes mellitus, insulin-dependent	Diabetes	1
Type 2 diabetes mellitus with ketoacidotic coma	Diabetes	1
Diabetes mellitus with no mention of complication	Diabetes	1
Type 1 diabetes mellitus with gangrene	Diabetes	1
Type 2 diabetes mellitus with hypoglycaemic coma	Diabetes	1
Type 2 diabetes mellitus with peripheral angiopathy	Diabetes	1
Type 1 diabetes mellitus	Diabetes	1
Non-insulin-dependent diabetes mellitus	Diabetes	1
Non-insulin dependent diabetes mellitus with hypoglyca coma	Diabetes	1
Diabetes mellitus NOS with unspecified complication	Diabetes	1

Read/OXMIS term	Disease category	Charlson score weight
Type 1 diabetes mellitus with hypoglycaemic coma	Diabetes	1
Diabetic annual review	Diabetes	1
Diabetes mellitus, juvenile ??? circulatory disorder	Diabetes	1
Unstable insulin dependent diabetes mellitus	Diabetes	1
Type 1 diabetes mellitus maturity onset	Diabetes	1
Other specified diabetes mellitus with ketoacidosis	Diabetes	1
Type II diabetes mellitus with persistent proteinuria	Diabetes	1
DIABETIC DIARRHOEA	Diabetes	1
HYPEROSMOLAR DIABETIC STATE	Diabetes	1
DIETARY CONTROL DIABETES	Diabetes	1
Type 2 diabetes mellitus - poor control	Diabetes	1
[X]Diabetes mellitus	Diabetes	1
Diabetes mellitus	Diabetes	1
Type 1 diabetes mellitus without complication	Diabetes	1
Diabetes mellitus NOS with no mention of complication	Diabetes	1
Diabetes mellitus NOS with ketoacidotic coma	Diabetes	1
Insulin dependent diab mell with peripheral angiopathy	Diabetes	1
Insulin dependent diabetes mellitus with hypoglycaemic coma	Diabetes	1
Diabetes mellitus with ketoacidosis	Diabetes	1
Insulin dependent diabetes mellitus - poor control	Diabetes	1
Type 2 diabetes mellitus - poor control	Diabetes	1
Diabetic - cooperative patient	Diabetes	1
Steroid induced diabetes mellitus without complication	Diabetes	1
Maturity onset diabetes	Diabetes	1
Type 1 diabetes mellitus	Diabetes	1
Admit diabetic emergency	Diabetes	1
LATENT DIABETES	Diabetes	1
H/O: diabetes mellitus	Diabetes	1
Type I diabetes mellitus - poor control	Diabetes	1
Insulin dependent diabetes mellitus	Diabetes	1
Diabetes mellitus, adult onset, no mention of complication	Diabetes	1
Type 2 diabetes mellitus with ulcer	Diabetes	1
Diabetes mellitus, adult onset, unspecified complication	Diabetes	1
Pre-existing diabetes mellitus, unspecified	Diabetes	1
Patient on maximal tolerated therapy for diabetes	Diabetes	1
Diabetes mellitus NOS with other specified manifestation	Diabetes	1
Diabetes mellitus with hyperosmolar coma	Diabetes	1
Malnutrition-related diabetes mellitus	Diabetes	1
IDDM-Insulin dependent diabetes mellitus	Diabetes	1
Diabetes mellitus NOS with ketoacidosis	Diabetes	1

Read/OXMIS term	Disease category	Charlson score weight
Type 2 diabetes mellitus with hypoglycaemic coma	Diabetes	1
Insulin dependent diabetes mellitus - poor control	Diabetes	1
PRECOMA DIABETIC	Diabetes	1
Type 1 diabetes mellitus with persistent proteinuria	Diabetes	1
DIABETES MELLITUS INSULIN DEPENDANT	Diabetes	1
Diabetes mellitus induced by non-steroid drugs	Diabetes	1
Diabetes mellitus with peripheral circulatory disorder	Diabetes	1
Maturity onset diabetes in youth type 2	Diabetes	1
IDDM with peripheral circulatory disorder	Diabetes	1
Type II diabetes mellitus with peripheral angiopathy	Diabetes	1
Type II diabetes mellitus with hypoglycaemic coma	Diabetes	1
Type 1 diabetes mellitus with persistent microalbuminuria	Diabetes	1
Non-insulin dependent diabetes mellitus	Diabetes	1
Type 2 diabetes mellitus with persistent microalbuminuria	Diabetes	1
[X]Other specified diabetes mellitus	Diabetes	1
Type 2 diabetes mellitus	Diabetes	1
Other specified diabetes mellitus with coma	Diabetes	1
Type II diabetes mellitus	Diabetes	1
Type I diabetes mellitus with ulcer	Diabetes	1
Type I diabetes mellitus with ketoacidotic coma	Diabetes	1
Non-insulin dependant diabetes mellitus - poor control	Diabetes	1
COMA DIABETIC	Diabetes	1
Diabetes mellitus, adult, other specified manifestation	Diabetes	1
Type I diabetes mellitus	Diabetes	1
Secondary diabetes mellitus	Diabetes	1
Type II diabetes mellitus - poor control	Diabetes	1
Diabetic - good control	Diabetes	1
Diabetes mellitus, juvenile type, no mention of complication	Diabetes	1
Diabetic cataract	Diabetes with complications	2
Type 2 diabetes mellitus with neurological complications	Diabetes with complications	2
Diabetes mellitus, juvenile type, with renal manifestation	Diabetes with complications	2
Type II diabetes mellitus with ophthalmic complications	Diabetes with complications	2
O/E - right eye background diabetic retinopathy	Diabetes with complications	2
Type I diabetes mellitus with polyneuropathy	Diabetes with complications	2
Insulin dependent diabetes mellitus with arthropathy	Diabetes with complications	2

Read/OXMIS term	Disease category	Charlson score weight
Non-insulin dependent diabetes mellitus with nephropathy	Diabetes with complications	2
Insulin dependent diabetes mellitus with mononeuropathy	Diabetes with complications	2
Diabetes mellitus, adult onset, neurological manifestation	Diabetes with complications	2
Insulin-dependent diabetes mellitus with renal complications	Diabetes with complications	2
Non-insulin dependent d m with neuropathic arthropathy	Diabetes with complications	2
Insulin-dependent diabetes mellitus with neurological comps	Diabetes with complications	2
Type 2 diabetes mellitus with ophthalmic complications	Diabetes with complications	2
O/E - left eye background diabetic retinopathy	Diabetes with complications	2
Type II diabetes mellitus with renal complications	Diabetes with complications	2
Preproliferative diabetic retinopathy	Diabetes with complications	2
Diabetes mellitus, juvenile type, ophthalmic manifestation	Diabetes with complications	2
Type 2 diabetes mellitus with gastroparesis	Diabetes with complications	2
Non-insulin-dependent diabetes mellitus with ophthalm comps	Diabetes with complications	2
NEUROPATHY DIABETIC	Diabetes with complications	2
Type 2 diabetes mellitus with diabetic cataract	Diabetes with complications	2
Type 1 diabetes mellitus with retinopathy	Diabetes with complications	2
Diabetes mellitus with polyneuropathy	Diabetes with complications	2
Diabetic retinopathy	Diabetes with complications	2
Type 2 diabetes mellitus with retinopathy	Diabetes with complications	2
Non-insulin dependent diabetes mellitus with polyneuropathy	Diabetes with complications	2
Non proliferative diabetic retinopathy	Diabetes with complications	2
Other specified diabetes mellitus with ophthalmic complicatn	Diabetes with complications	2
Type II diabetes mellitus with diabetic cataract	Diabetes with complications	2
Type 2 diabetes mellitus with polyneuropathy	Diabetes with complications	2
Type 2 diabetes mellitus with mononeuropathy	Diabetes with complications	2
Type II diabetes mellitus with retinopathy	Diabetes with complications	2
Type 1 diabetes mellitus with neurological complications	Diabetes with complications	2
Type I diabetes mellitus with mononeuropathy	Diabetes with complications	2

Read/OXMIS term	Disease category	Charlson score weight
Non-insulin-dependent diabetes mellitus with retinopathy	Diabetes with complications	2
Myasthenic syndrome due to diabetic amyotrophy	Diabetes with complications	2
Diabetes mellitus NOS with neurological manifestation	Diabetes with complications	2
Other specified diabetes mellitus with renal complications	Diabetes with complications	2
O/E - left eye proliferative diabetic retinopathy	Diabetes with complications	2
Type I diabetes mellitus with retinopathy	Diabetes with complications	2
Diabetic maculopathy	Diabetes with complications	2
DIABETIC GLOMERULOSCLEROSIS	Diabetes with complications	2
Type 2 diabetes mellitus with nephropathy	Diabetes with complications	2
Diabetic amyotrophy	Diabetes with complications	2
Kimmelstiel - Wilson disease	Diabetes with complications	2
Insulin dependent diabetes mellitus with nephropathy	Diabetes with complications	2
Type 1 diabetes mellitus with neurological complications	Diabetes with complications	2
Insulin-dependent diabetes mellitus with ophthalmic comps	Diabetes with complications	2
Diabetic mononeuropathy	Diabetes with complications	2
Diabetic neuropathy	Diabetes with complications	2
Advanced diabetic maculopathy	Diabetes with complications	2
Type II diabetes mellitus with renal complications	Diabetes with complications	2
O/E - left eye stable treated prolif diabetic retinopathy	Diabetes with complications	2
Type 2 diabetes mellitus with nephropathy	Diabetes with complications	2
Type 1 diabetes mellitus with diabetic cataract	Diabetes with complications	2
Type 2 diabetes mellitus with diabetic cataract	Diabetes with complications	2
Type I diabetes mellitus with nephropathy	Diabetes with complications	2
Type II diabetes mellitus with polyneuropathy	Diabetes with complications	2
Type 2 diabetes mellitus with neurological complications	Diabetes with complications	2
Type 1 diabetes mellitus with mononeuropathy	Diabetes with complications	2
Type 2 diabetes mellitus with neuropathic arthropathy	Diabetes with complications	2
High risk non proliferative diabetic retinopathy	Diabetes with complications	2

Read/OXMIS term	Disease category	Charlson score weight
Insulin dependent diabetes mellitus with retinopathy	Diabetes with complications	2
Type 1 diabetes mellitus with polyneuropathy	Diabetes with complications	2
CHARCOT'S DIABETIC ARTHROPATHY	Diabetes with complications	2
Polyneuropathy in disease NOS	Diabetes with complications	2
Type 2 diabetes mellitus with ophthalmic complications	Diabetes with complications	2
DIABETIC NEPHROPATHY	Diabetes with complications	2
O/E - diabetic maculopathy present both eyes	Diabetes with complications	2
Type 2 diabetes mellitus with renal complications	Diabetes with complications	2
Non-insulin-dependent diabetes mellitus with renal comps	Diabetes with complications	2
Non-insulin-dependent diabetes mellitus with neuro comps	Diabetes with complications	2
High risk proliferative diabetic retinopathy	Diabetes with complications	2
Diabetes mellitus with neuropathy	Diabetes with complications	2
O/E - left eye preproliferative diabetic retinopathy	Diabetes with complications	2
Non-insulin depend diabetes mellitus with diabetic cataract	Diabetes with complications	2
Type 2 diabetes mellitus with retinopathy	Diabetes with complications	2
Insulin dependent diabetes mellitus with polyneuropathy	Diabetes with complications	2
Type I diabetes mellitus with neurological complications	Diabetes with complications	2
Type 1 diabetes mellitus with renal complications	Diabetes with complications	2
Type II diabetes mellitus with neuropathic arthropathy	Diabetes with complications	2
Diabetes mellitus with neurological manifestation	Diabetes with complications	2
Type II diabetes mellitus with retinopathy	Diabetes with complications	2
Diabetic polyneuropathy	Diabetes with complications	2
O/E - right eye stable treated prolif diabetic retinopathy	Diabetes with complications	2
Diabetic retinopathy NOS	Diabetes with complications	2
Diabetes mellitus NOS with ophthalmic manifestation	Diabetes with complications	2
Diabetes mellitus, adult onset, ophthalmic manifestation	Diabetes with complications	2
Type 1 diabetes mellitus with nephropathy	Diabetes with complications	2
Type I diabetes mellitus with diabetic cataract	Diabetes with complications	2

Read/OXMIS term	Disease category	Charlson score weight
Type I diabetes mellitus with renal complications	Diabetes with complications	2
Type II diabetes mellitus with nephropathy	Diabetes with complications	2
Type 1 diabetes mellitus with renal complications	Diabetes with complications	2
Type II diabetes mellitus with mononeuropathy	Diabetes with complications	2
Diabetic amyotrophy	Diabetes with complications	2
Type II diabetes mellitus with nephropathy	Diabetes with complications	2
Type 1 diabetes mellitus with gastroparesis	Diabetes with complications	2
Non-insulin dependent diabetes mellitus with mononeuropathy	Diabetes with complications	2
Insulin dependent diabetes mellitus with diabetic cataract	Diabetes with complications	2
Diabetic nephropathy	Diabetes with complications	2
O/E - right eye preproliferative diabetic retinopathy	Diabetes with complications	2
Type 1 diabetes mellitus with neuropathic arthropathy	Diabetes with complications	2
Type II diabetes mellitus with polyneuropathy	Diabetes with complications	2
Other specified diabetes mellitus with neurological comps	Diabetes with complications	2
KIMMELSTIEL- WILSON DISEASE/SYNDROME	Diabetes with complications	2
Type 2 diabetes mellitus with neuropathic arthropathy	Diabetes with complications	2
Type 2 diabetes mellitus with renal complications	Diabetes with complications	2
Diabetes mellitus with ophthalmic manifestation	Diabetes with complications	2
Proliferative diabetic retinopathy	Diabetes with complications	2
Type II diabetes mellitus with neurological complications	Diabetes with complications	2
Diabetes mellitis with nephropathy NOS	Diabetes with complications	2
Type 1 diabetes mellitus with ophthalmic complications	Diabetes with complications	2
Flaccid paraplegia	Hemiplegia	2
SPASTIC PARAPLEGIA	Hemiplegia	2
Left hemiplegia	Hemiplegia	2
O/E - paraplegia	Hemiplegia	2
HYPERTENSIVE HEMIPLEGIA	Hemiplegia	2
PARAPLEGIA	Hemiplegia	2
Hemiplegia NOS	Hemiplegia	2
Congenital paraplegia	Hemiplegia	2
O/E - hemiplegia	Hemiplegia	2
HEMIPLEGIA FLACCID	Hemiplegia	2

Read/OXMIS term	Disease category	Charlson score weight
HEMIPLEGIA LEFT	Hemiplegia	2
Spastic hemiplegia	Hemiplegia	2
Right hemiplegia	Hemiplegia	2
Paraplegia - congenital	Hemiplegia	2
Spastic paraplegia	Hemiplegia	2
HEMIPLEGIA WITH HYPERTENSION	Hemiplegia	2
Paraplegia	Hemiplegia	2
PARALYSIS HEMIPLEGIA	Hemiplegia	2
Hereditary spastic paraplegia	Hemiplegia	2
HEMIPLEGIA RIGHT	Hemiplegia	2
Flaccid hemiplegia	Hemiplegia	2
Hemiplegia	Hemiplegia	2
SPASTIC HEMIPLEGIA	Hemiplegia	2
Secondary biliary cirrhosis	Mild liver disease	1
Fatty portal cirrhosis	Mild liver disease	1
Biliary cirrhosis NOS	Mild liver disease	1
Chronic hepatitis	Mild liver disease	1
Chronic hepatitis unspecified	Mild liver disease	1
Multilobular portal cirrhosis	Mild liver disease	1
Toxic liver disease with fibrosis and cirrhosis of liver	Mild liver disease	1
Pigmentary cirrhosis of liver	Mild liver disease	1
Laennec's cirrhosis, non-alcoholic	Mild liver disease	1
LIVER CIRRHOSIS	Mild liver disease	1
Chronic alcoholic hepatitis	Mild liver disease	1
Macronodular cirrhosis of liver	Mild liver disease	1
Chronic active hepatitis	Mild liver disease	1
Unilobular portal cirrhosis	Mild liver disease	1
HEPATITIS CHRONIC	Mild liver disease	1
SECONDARY BILIARY CIRRHOSIS (LIVER)	Mild liver disease	1
Portal cirrhosis unspecified	Mild liver disease	1
Non-alcoholic cirrhosis NOS	Mild liver disease	1
Alcoholic cirrhosis of liver	Mild liver disease	1
Pipe-stem portal cirrhosis	Mild liver disease	1
Portal cirrhosis	Mild liver disease	1
Diffuse nodular cirrhosis	Mild liver disease	1
PRIMARY BILIARY CIRRHOSIS (LIVER)	Mild liver disease	1
HEPATITIS CHRONIC ACTIVE	Mild liver disease	1
CIRRHOSIS	Mild liver disease	1
MICRONODULAR CIRRHOSIS	Mild liver disease	1
Xanthomatous portal cirrhosis	Mild liver disease	1
Cirrhosis of liver NOS	Mild liver disease	1
Recurrent hepatitis	Mild liver disease	1
[X]Other and unspecified cirrhosis of liver	Mild liver disease	1
Cirrhosis and chronic liver disease	Mild liver disease	1
Syphilitic portal cirrhosis	Mild liver disease	1

Read/OXMIS term	Disease category	Charlson score weight
Glycogenosis with hepatic cirrhosis	Mild liver disease	1
CIRRHOSIS ALCOHOLIC	Mild liver disease	1
Cryptogenic cirrhosis of liver	Mild liver disease	1
Primary biliary cirrhosis	Mild liver disease	1
Biliary cirrhosis	Mild liver disease	1
Cirrhosis - non alcoholic	Mild liver disease	1
Hepatitis unspecified	Mild liver disease	1
Cardiac portal cirrhosis	Mild liver disease	1
Chronic persistent hepatitis	Mild liver disease	1
Acute yellow atrophy	Mild liver disease	1
Toxic portal cirrhosis	Mild liver disease	1
MACRONODULAR CIRRHOSIS	Mild liver disease	1
HEPATITIS CHRONIC AGGRESSIVE	Mild liver disease	1
Portal fibrosis without cirrhosis	Mild liver disease	1
Chronic aggressive hepatitis	Mild liver disease	1
Subacute yellow atrophy	Mild liver disease	1
Postnecrotic cirrhosis of liver	Mild liver disease	1
Florid cirrhosis	Mild liver disease	1
Chronic hepatitis NOS	Mild liver disease	1
Oesophageal varices in alcoholic cirrhosis of the liver	Mod liver disease	3
Liver abscess and chronic liver disease causing sequelae NOS	Mod liver disease	3
Oesophageal varices without bleeding	Mod liver disease	3
[X]Oesophageal varices in diseases classified elsewhere	Mod liver disease	3
Other sequelae of chronic liver disease	Mod liver disease	3
Oesophageal varices with bleeding in diseases EC	Mod liver disease	3
SYNDROME HEPATORENAL	Mod liver disease	3
Hepatorenal syndrome	Mod liver disease	3
PORTAL HYPERTENSION	Mod liver disease	3
Oesophageal varices with bleeding	Mod liver disease	3
Oesophageal varices in diseases EC	Mod liver disease	3
Hepatic coma	Mod liver disease	3
Oesophageal varices NOS	Mod liver disease	3
Oesophageal varices	Mod liver disease	3
Portal hypertension	Mod liver disease	3
Oesophageal varices in cirrhosis of the liver	Mod liver disease	3
Other specified viral hepatitis with hepatic coma NOS	Mod liver disease	3
Rigid oesophagoscopic injection sclerotherapy oesoph varices	Mod liver disease	3
HEPATIC COMA	Mod liver disease	3
Oesophageal varices without bleeding in diseases EC	Mod liver disease	3
Oesophageal varices in diseases EC NOS	Mod liver disease	3
Other specified anterior myocardial infarction	Myocardial infarction	1

Read/OXMIS term	Disease category	Charlson score weight
Acute myocardial infarction NOS	Myocardial infarction	1
Heart attack	Myocardial infarction	1
MI - acute myocardial infarction	Myocardial infarction	1
Lateral myocardial infarction NOS	Myocardial infarction	1
THROMBOSIS CORONARY	Myocardial infarction	1
Acute subendocardial infarction	Myocardial infarction	1
H/O: Myocardial infarction in last year	Myocardial infarction	1
Other acute myocardial infarction	Myocardial infarction	1
Acute inferoposterior infarction	Myocardial infarction	1
CORONARY INFARCTION	Myocardial infarction	1
Acute myocardial infarction	Myocardial infarction	1
Acute anterolateral infarction	Myocardial infarction	1
Personal history of myocardial infarction	Myocardial infarction	1
Acute ST segment elevation myocardial infarction	Myocardial infarction	1
Cardiac rupture following myocardial infarction (MI)	Myocardial infarction	1
Acute non-ST segment elevation myocardial infarction	Myocardial infarction	1
Acute non-Q wave infarction	Myocardial infarction	1
Acute anteroseptal infarction	Myocardial infarction	1
Old myocardial infarction	Myocardial infarction	1
Silent myocardial infarction	Myocardial infarction	1
Healed myocardial infarction	Myocardial infarction	1
Coronary thrombosis	Myocardial infarction	1
HEART ATTACK	Myocardial infarction	1
Other acute myocardial infarction NOS	Myocardial infarction	1
Acute inferolateral infarction	Myocardial infarction	1
Acute duodenal ulcer unspecified	Peptic ulcer disease	1
Endoscopic injection haemostasis of gastric ulcer	Peptic ulcer disease	1
Unspecified gastrojejunal ulcer with obstruction	Peptic ulcer disease	1
Peptic ulcer - (PU) site unspecified	Peptic ulcer disease	1
ULCER STOMACH PERFORATED	Peptic ulcer disease	1
Peptic ulcer of oesophagus	Peptic ulcer disease	1
ULCER GASTROJEJUNAL	Peptic ulcer disease	1
Unspecified duodenal ulcer NOS	Peptic ulcer disease	1
EXCISION PEPTIC ULCER	Peptic ulcer disease	1
Pyloric ulcer	Peptic ulcer disease	1
ULCER GASTRIC PERFORATED	Peptic ulcer disease	1
Chronic gastrojejunal ulcer with perforation	Peptic ulcer disease	1
Acute gastric ulcer	Peptic ulcer disease	1
Unspecified duodenal ulcer	Peptic ulcer disease	1
Chronic duodenal ulcer unspecified	Peptic ulcer disease	1
Bleeding acute gastric ulcer	Peptic ulcer disease	1
Unspec gastric ulcer; unspec haemorrhage and/or perforation	Peptic ulcer disease	1
ULCER DUODENUM	Peptic ulcer disease	1
Chronic gastric ulcer unspecified	Peptic ulcer disease	1

Read/OXMIS term	Disease category	Charlson score weight
Chronic gastric ulcer with haemorrhage	Peptic ulcer disease	1
Stomal ulcer	Peptic ulcer disease	1
Chronic peptic ulcer unspecified	Peptic ulcer disease	1
Acute gastric ulcer unspecified	Peptic ulcer disease	1
Peptic ulcer NOS	Peptic ulcer disease	1
Prepyloric ulcer	Peptic ulcer disease	1
Acute gastric ulcer with haemorrhage and perforation	Peptic ulcer disease	1
Operation on gastric ulcer NOS	Peptic ulcer disease	1
Unspecified gastrojejunal ulcer with haemorrhage	Peptic ulcer disease	1
Chronic duodenal ulcer with obstruction	Peptic ulcer disease	1
Acute peptic ulcer NOS	Peptic ulcer disease	1
Unspecified duodenal ulcer with obstruction	Peptic ulcer disease	1
Unspecified gastric ulcer with haemorrhage	Peptic ulcer disease	1
Acute gastrojejunal ulcer with obstruction	Peptic ulcer disease	1
Unspecified duodenal ulcer without mention of complication	Peptic ulcer disease	1
Duodenal ulcer disease	Peptic ulcer disease	1
Chronic duodenal ulcer without mention of complication	Peptic ulcer disease	1
Unspecified gastrojejunal ulcer with perforation	Peptic ulcer disease	1
Gastric ulcer - (GU)	Peptic ulcer disease	1
Chronic gastrojejunal ulcer unspecified	Peptic ulcer disease	1
ULCER GASTROJEJUNAL PERFORATED	Peptic ulcer disease	1
Chronic gastrojejunal ulcer with haemorrhage and perforation	Peptic ulcer disease	1
Unspecified gastric ulcer with obstruction	Peptic ulcer disease	1
Unspecified peptic ulcer	Peptic ulcer disease	1
Chronic peptic ulcer	Peptic ulcer disease	1
Acute duodenal ulcer NOS	Peptic ulcer disease	1
Acute gastrojejunal ulcer without mention of complication	Peptic ulcer disease	1
Acute gastric ulcer with perforation	Peptic ulcer disease	1
Chronic gastric ulcer with obstruction	Peptic ulcer disease	1
Chronic duodenal ulcer	Peptic ulcer disease	1
Unspec gastrojejunal ulcer; unspec haemorrhage/perforation	Peptic ulcer disease	1
Gastrocolic ulcer	Peptic ulcer disease	1
Acute peptic ulcer	Peptic ulcer disease	1
Unspecified gastric ulcer with perforation	Peptic ulcer disease	1
Acute duodenal ulcer with haemorrhage and perforation	Peptic ulcer disease	1
ULCER PEPTIC DUODENUM	Peptic ulcer disease	1
Operations on duodenal ulcer	Peptic ulcer disease	1
Acute duodenal ulcer with haemorrhage	Peptic ulcer disease	1
ULCER PEPTIC DUODENUM PERFORATED	Peptic ulcer disease	1
Unspecified peptic ulcer with haemorrhage and perforation	Peptic ulcer disease	1

Read/OXMIS term	Disease category	Charlson score weight
Unspec gastrojejunal ulcer with haemorrhage and perforation	Peptic ulcer disease	1
ULCER PEPTIC STOMACH PERFORATED	Peptic ulcer disease	1
Chronic peptic ulcer with haemorrhage and perforation	Peptic ulcer disease	1
Bleeding chronic gastric ulcer	Peptic ulcer disease	1
Closure of perforated gastric ulcer	Peptic ulcer disease	1
Acute duodenal ulcer with perforation	Peptic ulcer disease	1
Acute peptic ulcer with perforation	Peptic ulcer disease	1
Suture of ulcer of stomach NEC	Peptic ulcer disease	1
Acute gastrojejunal ulcer with haemorrhage	Peptic ulcer disease	1
Unspecified duodenal ulcer with perforation	Peptic ulcer disease	1
Chronic gastric ulcer NOS	Peptic ulcer disease	1
ULCER DUODENAL RECURRANCE	Peptic ulcer disease	1
Unspecified gastric ulcer NOS	Peptic ulcer disease	1
Gastrojejunal ulcer NOS	Peptic ulcer disease	1
Unspecified gastrojejunal ulcer without mention complication	Peptic ulcer disease	1
Gastric ulcer NOS	Peptic ulcer disease	1
Unspecified gastrojejunal ulcer	Peptic ulcer disease	1
Chronic gastrojejunal ulcer NOS	Peptic ulcer disease	1
Unspec peptic ulcer; unspec haemorrhage and/or perforation	Peptic ulcer disease	1
Balfour excision of gastric ulcer	Peptic ulcer disease	1
Unspec duodenal ulcer; unspec haemorrhage and/or perforation	Peptic ulcer disease	1
Chronic gastric ulcer without mention of complication	Peptic ulcer disease	1
Acute gastric ulcer without mention of complication	Peptic ulcer disease	1
Acute peptic ulcer without mention of complication	Peptic ulcer disease	1
ULCER PEPTIC PERFORATED	Peptic ulcer disease	1
Chronic gastric ulcer with haemorrhage and perforation	Peptic ulcer disease	1
Acute gastrojejunal ulcer with haemorrhage and perforation	Peptic ulcer disease	1
Unspecified peptic ulcer without mention of complication	Peptic ulcer disease	1
Gastrojejunal ulcer (GJU)	Peptic ulcer disease	1
Unspecified gastric ulcer	Peptic ulcer disease	1
Peptic ulcer symptoms	Peptic ulcer disease	1
Acute duodenal ulcer	Peptic ulcer disease	1
Acute peptic ulcer with obstruction	Peptic ulcer disease	1
Chronic gastrojejunal ulcer with obstruction	Peptic ulcer disease	1
Unspecified peptic ulcer with haemorrhage	Peptic ulcer disease	1
Acute duodenal ulcer without mention of complication	Peptic ulcer disease	1
Chronic duodenal ulcer with haemorrhage and perforation	Peptic ulcer disease	1
Closure of perforated duodenal ulcer	Peptic ulcer disease	1

Read/OXMIS term	Disease category	Charlson score weight
Chronic peptic ulcer NOS	Peptic ulcer disease	1
Stress ulcer NOS	Peptic ulcer disease	1
Acute peptic ulcer unspecified	Peptic ulcer disease	1
Anti-platelet induced gastric ulcer	Peptic ulcer disease	1
Acute gastric ulcer NOS	Peptic ulcer disease	1
Chronic gastric ulcer	Peptic ulcer disease	1
Acute gastric ulcer with obstruction	Peptic ulcer disease	1
Chronic duodenal ulcer NOS	Peptic ulcer disease	1
ULCER PEPTIC	Peptic ulcer disease	1
Chronic peptic ulcer without mention of complication	Peptic ulcer disease	1
Duodenal ulcer - (DU)	Peptic ulcer disease	1
Chronic gastrojejunal ulcer	Peptic ulcer disease	1
Unspecified gastric ulcer without mention of complication	Peptic ulcer disease	1
Chronic gastric ulcer with perforation	Peptic ulcer disease	1
Duodenal erosion	Peptic ulcer disease	1
REPAIR PERFORATED GASTRIC ULCER	Peptic ulcer disease	1
Unspecified peptic ulcer with obstruction	Peptic ulcer disease	1
Closure of gastric ulcer NEC	Peptic ulcer disease	1
Chronic peptic ulcer with obstruction	Peptic ulcer disease	1
ULCER MARGINAL	Peptic ulcer disease	1
Multiple gastric ulcers	Peptic ulcer disease	1
Unspecified gastrojejunal ulcer NOS	Peptic ulcer disease	1
[V]Personal history of peptic ulcer	Peptic ulcer disease	1
Acute peptic ulcer with haemorrhage	Peptic ulcer disease	1
Resection of gastric ulcer by cautery	Peptic ulcer disease	1
Acute duodenal ulcer with obstruction	Peptic ulcer disease	1
[V] Personal history of gastric ulcer	Peptic ulcer disease	1
ULCER PEPTIC STOMACH	Peptic ulcer disease	1
Unspecified duodenal ulcer with haemorrhage and perforation	Peptic ulcer disease	1
Unspecified peptic ulcer NOS	Peptic ulcer disease	1
Stomach ulcer operations	Peptic ulcer disease	1
ULCER DUODENUM PERFORATED	Peptic ulcer disease	1
Perforated chronic gastric ulcer	Peptic ulcer disease	1
Duodenal ulcer NOS	Peptic ulcer disease	1
Acute gastrojejunal ulcer with perforation	Peptic ulcer disease	1
Chronic peptic ulcer with haemorrhage	Peptic ulcer disease	1
Chronic gastrojejunal ulcer without mention of complication	Peptic ulcer disease	1
Chronic peptic ulcer with perforation	Peptic ulcer disease	1
Recurrent duodenal ulcer	Peptic ulcer disease	1
REPAIR PERFORATED PEPTIC ULCER	Peptic ulcer disease	1
Acute peptic ulcer with haemorrhage and perforation	Peptic ulcer disease	1
Unspecified gastric ulcer with haemorrhage and perforation	Peptic ulcer disease	1

Read/OXMIS term	Disease category	Charlson score weight
Chronic gastrojejunal ulcer with haemorrhage	Peptic ulcer disease	1
Bleeding chronic duodenal ulcer	Peptic ulcer disease	1
ULCER PREPYLORIC	Peptic ulcer disease	1
Other specified operation on gastric ulcer	Peptic ulcer disease	1
Acute gastrojejunal ulcer NOS	Peptic ulcer disease	1
Acute gastrojejunal ulcer unspecified	Peptic ulcer disease	1
Unspecified peptic ulcer with perforation	Peptic ulcer disease	1
Acute gastric ulcer with haemorrhage	Peptic ulcer disease	1
ULCER STOMACH	Peptic ulcer disease	1
DUODENAL ULCER BLEEDING	Peptic ulcer disease	1
Operations on gastric ulcer	Peptic ulcer disease	1
Acute gastrojejunal ulcer	Peptic ulcer disease	1
Juxtarenal aortic aneurysm	Peripheral vascular disease	1
Tube graft abdominal Aortic aneurysm (emergency)	Peripheral vascular disease	1
[D]Gangrene	Peripheral vascular disease	1
Ruptured aortic aneurysm NOS	Peripheral vascular disease	1
H/O: aortic aneurysm	Peripheral vascular disease	1
Other peripheral vascular disease	Peripheral vascular disease	1
[X]Aortic aneurysm of unspecified site, ruptured	Peripheral vascular disease	1
Dissecting aortic aneurysm	Peripheral vascular disease	1
Other specified peripheral vascular disease	Peripheral vascular disease	1
Presenile gangrene	Peripheral vascular disease	1
Ruptured suprarenal aortic aneurysm	Peripheral vascular disease	1
Thoracoabdominal aortic aneurysm, ruptured	Peripheral vascular disease	1
Aortic aneurysm	Peripheral vascular disease	1
[D]Gangrene of toe in diabetic	Peripheral vascular disease	1
Gangrene of toe	Peripheral vascular disease	1
INTERMITTENT CLAUDICATION	Peripheral vascular disease	1
Peripheral gangrene	Peripheral vascular disease	1
Thoracoabdominal aortic aneurysm, without mention of rupture	Peripheral vascular disease	1
Gangrene of hand	Peripheral vascular disease	1
GANGRENE TOE	Peripheral vascular disease	1
Emergency repair of aortic aneurysm	Peripheral vascular disease	1

Read/OXMIS term	Disease category	Charlson score weight
Y graft abdominal Aortic aneurysm	Peripheral vascular disease	1
Other specified peripheral vascular disease NOS	Peripheral vascular disease	1
Diabetes with gangrene	Peripheral vascular disease	1
GANGRENE FOOT	Peripheral vascular disease	1
SCROTAL GANGRENE	Peripheral vascular disease	1
[D]Widespread diabetic foot gangrene	Peripheral vascular disease	1
O/E - gangrene	Peripheral vascular disease	1
Inflammatory abdominal aortic aneurysm	Peripheral vascular disease	1
Gangrene of foot	Peripheral vascular disease	1
Gangrene of finger	Peripheral vascular disease	1
[D]Gangrene NOS	Peripheral vascular disease	1
Intermittent claudication	Peripheral vascular disease	1
Aortic aneurysm without mention of rupture NOS	Peripheral vascular disease	1
DISSECTION AORTA	Peripheral vascular disease	1
Claudication	Peripheral vascular disease	1
Y graft of abdominal Aortic aneurysm (emergency)	Peripheral vascular disease	1
Thoracic aortic aneurysm without mention of rupture	Peripheral vascular disease	1
Peripheral ischaemic vascular disease	Peripheral vascular disease	1
ULCER WITH GANGRENE	Peripheral vascular disease	1
Thoracic aortic aneurysm which has ruptured	Peripheral vascular disease	1
Peripheral vascular disease NOS	Peripheral vascular disease	1
Peripheral vascular disease NOS	Peripheral vascular disease	1
Aortic aneurysm NOS	Peripheral vascular disease	1
Abdominal aortic aneurysm which has ruptured	Peripheral vascular disease	1
Aortic aneurysm repair	Peripheral vascular disease	1
AORTIC ANEURYSM	Peripheral vascular disease	1
H/O: Peripheral vascular disease procedure	Peripheral vascular disease	1
Aortic aneurysm	Peripheral vascular disease	1

Read/OXMIS term	Disease category	Charlson score weight
Ruptured abdominal aortic aneurysm	Peripheral vascular disease	1
[X]Aortic aneurysm of unspecified site, nonruptured	Peripheral vascular disease	1
Gangrene of thumb	Peripheral vascular disease	1
[D]Gangrene, spreading cutaneous	Peripheral vascular disease	1
AAA - Abdominal aortic aneurysm without mention of rupture	Peripheral vascular disease	1
Abdominal aortic aneurysm without mention of rupture	Peripheral vascular disease	1
[X]Other specified peripheral vascular diseases	Peripheral vascular disease	1
Leaking abdominal aortic aneurysm	Peripheral vascular disease	1
Tube graft of Abdominal aortic aneurysm	Peripheral vascular disease	1
PVD (PERIPHERAL VASCULAR DISEASE)	Peripheral vascular disease	1
GANGRENE	Peripheral vascular disease	1
SYMMETRICAL GANGRENE EXTREMITIES	Peripheral vascular disease	1
Ruptured thoracic aortic aneurysm	Peripheral vascular disease	1
RENAL MEDULLARY NECROSIS	Renal disease	2
Phosphate-losing tubular disorders	Renal disease	2
Nephritis unsp????? glomerulonephritis lesion NOS	Renal disease	2
Renal dwarfism	Renal disease	2
MESANGIOCAPILLARY GLOMERULONEPHRITIS	Renal disease	2
Acute renal failure NOS	Renal disease	2
OSTEODYSTROPHY URAEMIC	Renal disease	2
Acute pyelonephritis with medullary necrosis	Renal disease	2
Chronic glomerulonephritis NOS	Renal disease	2
Impaired renal function	Renal disease	2
Chronic membranous glomerulonephritis	Renal disease	2
Chronic rapidly progressive glomerulonephritis	Renal disease	2
RENAL DISEASE	Renal disease	2
MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS	Renal disease	2
Nephritis unsp membranoprolif glomerulonephritis lesion	Renal disease	2
Chronic kidney disease stage 2	Renal disease	2
NEPHRITIS	Renal disease	2
Acute renal cortical necrosis	Renal disease	2
Mesangioproliferative glomerulonephritis NEC	Renal disease	2
GLOMERULONEPHRITIS CHRONIC	Renal disease	2
Nephritis, nephrosis and nephrotic syndrome	Renal disease	2
Nephropathy – chronic	Renal disease	2

Read/OXMIS term	Disease category	Charlson score weight
Other impaired renal function disorder NOS	Renal disease	2
OSTEODYSTROPHY AZOTAEMIC	Renal disease	2
NEPHROPATHY MEMBRANOUS	Renal disease	2
Nephrogenic diabetes insipidus	Renal disease	2
Renal osteodystrophy	Renal disease	2
Chron neph syn difuse endocap prolifrativ glomerulonephritis	Renal disease	2
Renal failure unspecified	Renal disease	2
Chron nephritic syndrom difuse membranous glomerulonephritis	Renal disease	2
Renal cortical necrosis unspecified	Renal disease	2
Chronic focal glomerulonephritis	Renal disease	2
CHRONIC RENAL FAILURE	Renal disease	2
NEPHRITIS HEREDITARY	Renal disease	2
Nephritis and nephropathy unspecified	Renal disease	2
Chronic renal failure	Renal disease	2
[X]Heredtry nephrpthy NEC difus mesangiocapilry glomneph	Renal disease	2
Acute pyelonephritis without medullary necrosis	Renal disease	2
Chronic glomerulonephritis	Renal disease	2
Renal rickets	Renal disease	2
OSTEODYSTROPHY RENAL	Renal disease	2
NEPHROPATHY HYPOKALAEMIC	Renal disease	2
Chronic kidney disease stage 4	Renal disease	2
Membranoproliferative nephritis unspecified	Renal disease	2
Nephrotic syndrome??????? glomerulonephritis	Renal disease	2
Chron neph syn difus mesangial prolifrtiv glomerulonephritis	Renal disease	2
Chronic kidney disease stage 5	Renal disease	2
[X]Renal failure	Renal disease	2
Impaired renal function disorder NOS	Renal disease	2
End stage renal failure	Renal disease	2
RENAL FAILURE	Renal disease	2
Chronic pyelonephritis without medullary necrosis	Renal disease	2
Other acute renal failure	Renal disease	2
H/O: nephritis	Renal disease	2
Nephritis – chronic	Renal disease	2
Chronic kidney disease stage 1	Renal disease	2
Focal membranoproliferative glomerulonephritis	Renal disease	2
CHRONIC NEPHRITIS	Renal disease	2
Nephritis and nephropathy unspecified	Renal disease	2
Acute renal medullary necrosis	Renal disease	2
Chronic membranoproliferative glomerulonephritis	Renal disease	2
Mesangiocapillary glomerulonephritis NEC	Renal disease	2
Renal infantilism	Renal disease	2
Acute nephritis with lesions of necrotising glomerulitis	Renal disease	2
Chronic kidney disease stage 3	Renal disease	2

Read/OXMIS term	Disease category	Charlson score weight
Other chronic glomerulonephritis NOS	Renal disease	2
Chronic diffuse glomerulonephritis	Renal disease	2
Renal osteodystrophy NOS	Renal disease	2
Nephrotic syn,diffuse mesangiocapillary glomerulonephritis	Renal disease	2
Renal medullary necrosis unspecified	Renal disease	2
Chronic nephritic syn diffuse crescentic glomerulonephritis	Renal disease	2
Hypokalaemic nephropathy	Renal disease	2
[X]Other chronic renal failure	Renal disease	2
Chronic neph syn difus mesangiocapillary glomerulonephritis	Renal disease	2
Chronic glomerulonephritis diseases EC	Renal disease	2
Chronic pyelonephritis with medullary necrosis	Renal disease	2
[X]Other acute renal failure	Renal disease	2
LUPUS ERYTHEMATOSUS SYSTEMIC	Rheumatological disease	1
Felty's syndrome	Rheumatological disease	1
RHEUMATISM	Rheumatological disease	1
RHEUMATISM NONARTICULAR	Rheumatological disease	1
RHEUMATOID ARTHRITIS	Rheumatological disease	1
[X]Rheumatoid arthritis?????? organs or systems	Rheumatological disease	1
Systemic sclerosis induced by drugs and chemicals	Rheumatological disease	1
Caplan's syndrome	Rheumatological disease	1
RHEUMATOID ARTHRITIS SPINE	Rheumatological disease	1
Progressive systemic sclerosis	Rheumatological disease	1
Systemic sclerosis	Rheumatological disease	1
Rheumatoid arthritis of hip	Rheumatological disease	1
Systemic lupus erythematosus with organ or sys involv	Rheumatological disease	1
Fibrosing alveolitis associated with rheumatoid arthritis	Rheumatological disease	1
Seropositive errosive rheumatoid arthritis	Rheumatological disease	1
Systemic lupus erythematosus	Rheumatological disease	1
Rheumatoid arthritis of other tarsal joint	Rheumatological disease	1
LUPUS ERYTHEMATOSUS ACUTE	Rheumatological disease	1
Seropositive rheumatoid arthritis, unspecified	Rheumatological disease	1
[X]Seropositive rheumatoid arthritis, unspecified	Rheumatological disease	1

Read/OXMIS term	Disease category	Charlson score weight
Rheumatoid arthritis of DIP joint of finger	Rheumatological disease	1
Rheumatoid arthritis of sternoclavicular joint	Rheumatological disease	1
Rheumatism unspecified	Rheumatological disease	1
Muscular rheumatism	Rheumatological disease	1
SERO POSITIVE RHEUMATOID ARTHRITIS	Rheumatological disease	1
Giant cell arteritis with polymyalgia rheumatica	Rheumatological disease	1
Polymyalgia rheumatica	Rheumatological disease	1
SCLERODERMA DIFFUSE	Rheumatological disease	1
Rheumatoid arthritis of PIP joint of finger	Rheumatological disease	1
Libman-Sacks disease	Rheumatological disease	1
SYSTEMIC LUPUS ERYTHEMATOSUS WITH RENAL	Rheumatological disease	1
Systemic lupus erythematosus with pericarditis	Rheumatological disease	1
Rheumatoid arthritis of IP joint of toe	Rheumatological disease	1
Rheumatoid arthritis of MCP joint	Rheumatological disease	1
Other specified nonarticular rheumatism	Rheumatological disease	1
Lung disease with systemic sclerosis	Rheumatological disease	1
Rheumatoid arthritis and other inflammatory polyarthropathy	Rheumatological disease	1
Seronegative rheumatoid arthritis	Rheumatological disease	1
RHEUMATISM MUSCULAR ARM	Rheumatological disease	1
Rheumatoid carditis	Rheumatological disease	1
SCLERODERMA ACROSCLEROTIC	Rheumatological disease	1
Lung disease with systemic lupus erythematosus	Rheumatological disease	1
Lupus nephritis	Rheumatological disease	1
Acrosclerosis	Rheumatological disease	1
POLYMYOSITIS	Rheumatological disease	1
RHEUMATOID ARTHRITIS INCREASED ACTIVITY	Rheumatological disease	1
Disseminated lupus erythematosus	Rheumatological disease	1
Flare of rheumatoid arthritis	Rheumatological disease	1

Read/OXMIS term	Disease category	Charlson score weight
Rheumatoid arthritis	Rheumatological disease	1
Sero negative polyarthritis	Rheumatological disease	1
[X]Other forms of systemic sclerosis	Rheumatological disease	1
SERO NEGATIVE RHEUMATOID ARTHRITIS	Rheumatological disease	1
Rheumatism or fibrositis NOS	Rheumatological disease	1
SYNDROME FELTY'S	Rheumatological disease	1
RHEUMATISM HANDS	Rheumatological disease	1
Rheumatoid arthritis of lesser MTP joint	Rheumatological disease	1
Polymyositis ossificans	Rheumatological disease	1
SCLERODERMA	Rheumatological disease	1
[X]Other specified rheumatoid arthritis	Rheumatological disease	1
MONOARTICULAR RHEUMATISM	Rheumatological disease	1
Myopathy due to scleroderma	Rheumatological disease	1
Myopathy due to rheumatoid arthritis	Rheumatological disease	1
Rheumatoid lung disease	Rheumatological disease	1
Rheumatoid arthritis of subtalar joint	Rheumatological disease	1
LIBMAN- SACKS DISEASE	Rheumatological disease	1
Rheumatoid arthritis of shoulder	Rheumatological disease	1
Rheumatoid arthritis of talonavicular joint	Rheumatological disease	1
Rheumatoid arthritis of knee	Rheumatological disease	1
RHEUMATISM HANDS ACUTE	Rheumatological disease	1
Rheumatoid arthritis of ankle	Rheumatological disease	1
Endemic polyarthritis	Rheumatological disease	1
[X]Other forms of systemic lupus erythematosus	Rheumatological disease	1
[X]Other seropositive rheumatoid arthritis	Rheumatological disease	1
RHEUMATISM NONARTICULAR SHOULDER	Rheumatological disease	1
Polymyositis	Rheumatological disease	1
Lung disease with polymyositis	Rheumatological disease	1

Read/OXMIS term	Disease category	Charlson score weight
Rheumatoid arthritis of tibio-fibular joint	Rheumatological disease	1
Rheumatoid arthritis of distal radio-ulnar joint	Rheumatological disease	1
Rheumatism and fibrositis unspecified	Rheumatological disease	1
Rheumatoid arthritis of sacro-iliac joint	Rheumatological disease	1
Myopathy due to disseminated lupus erythematosus	Rheumatological disease	1
LUPUS ERYTHEMATOSUS DISSEMINATED	Rheumatological disease	1
SCLERODERMA GENERALIZED	Rheumatological disease	1
Rheumatoid arthritis of 1st MTP joint	Rheumatological disease	1
Scleroderma	Rheumatological disease	1
Nonarticular rheumatism NOS	Rheumatological disease	1
POLYMYALGIA RHEUMATICA	Rheumatological disease	1
Rheumatoid arthritis of elbow	Rheumatological disease	1
Drug-induced systemic lupus erythematosus	Rheumatological disease	1
Nephrotic syndrome in systemic lupus erythematosus	Rheumatological disease	1
Rheumatoid lung	Rheumatological disease	1
Systemic lupus erythematosus NOS	Rheumatological disease	1
Rheumatoid arthritis of wrist	Rheumatological disease	1
Hand rheumatism	Rheumatological disease	1
RHEUMATISM MUSCULAR	Rheumatological disease	1
Rheumatoid arthritis of acromioclavicular joint	Rheumatological disease	1
Rheumatoid lung	Rheumatological disease	1
ACROSCLEROSIS	Rheumatological disease	1
ACUTE SYSTEMIC LUPUS ERYTHEMATOSUS	Rheumatological disease	1
Polyneuropathy in rheumatoid arthritis	Rheumatological disease	1
SYSTEMIC LUPUS ERYTHEMATOSUS	Rheumatological disease	1
RHEUMATIC ARTHRITIS	Rheumatological disease	1

(Note) OXMIS: Oxford Medical Information System; [X]: examine procedure; NOS: Not Otherwise Specified; ????: any available character (four); OS: Otherwise Specified; H/O: History of; EC: enterocolitis; NEC: Necrotizing enterocolitis; AIDS: acquired immunodeficiency syndrome

Appendix 22. Chapter 6: ICD-10 codes for Charlson Comorbidity Index

ICD-10	Description	Weight
I25.2	Myocardial infarction	1
I09.9	Congestive heart failure	1
I11.0	Congestive heart failure	1
I13.0	Congestive heart failure	1
I13.2	Congestive heart failure	1
I25.5	Congestive heart failure	1
I42.0	Congestive heart failure	1
I42.5	Congestive heart failure	1
I42.6	Congestive heart failure	1
I42.7	Congestive heart failure	1
I42.8	Congestive heart failure	1
I42.9	Congestive heart failure	1
P29.0	Congestive heart failure	1
I73.1	Peripheral vascular disease	1
I73.8	Peripheral vascular disease	1
I73.9	Peripheral vascular disease	1
I77.1	Peripheral vascular disease	1
I79.0	Peripheral vascular disease	1
I79.2	Peripheral vascular disease	1
K55.1	Peripheral vascular disease	1
K55.8	Peripheral vascular disease	1
K55.9	Peripheral vascular disease	1
Z95.8	Peripheral vascular disease	1
Z95.9	Peripheral vascular disease	1
H34.0	Cerebrovascular disease	1
F05.1	Dementia	1
G31.1	Dementia	1
I27.8	Chronic pulmonary disease	1
I27.9	Chronic pulmonary disease	1
J68.4	Chronic pulmonary disease	1
J70.1	Chronic pulmonary disease	1
J70.3	Chronic pulmonary disease	1
M31.5	Rheumatic disease	1
M35.1	Rheumatic disease	1
M35.3	Rheumatic disease	1
M36.0	Rheumatic disease	1
K70.0	Mild liver disease	1
K70.1	Mild liver disease	1
K70.2	Mild liver disease	1
K70.3	Mild liver disease	1
K70.9	Mild liver disease	1
K71.3	Mild liver disease	1
K71.4	Mild liver disease	1
K71.5	Mild liver disease	1
K71.7	Mild liver disease	1

ICD-10	Description	Weight
K76.0	Mild liver disease	1
K76.2	Mild liver disease	1
K76.3	Mild liver disease	1
K76.4	Mild liver disease	1
K76.8	Mild liver disease	1
K76.9	Mild liver disease	1
Z94.4	Mild liver disease	1
E10.0	Diabetes without chronic complication	1
E10.1	Diabetes without chronic complication	1
E10.6	Diabetes without chronic complication	1
E10.8	Diabetes without chronic complication	1
E10.9	Diabetes without chronic complication	1
E11.0	Diabetes without chronic complication	1
E11.1	Diabetes without chronic complication	1
E11.6	Diabetes without chronic complication	1
E11.8	Diabetes without chronic complication	1
E11.9	Diabetes without chronic complication	1
E12.0	Diabetes without chronic complication	1
E12.1	Diabetes without chronic complication	1
E12.6	Diabetes without chronic complication	1
E12.8	Diabetes without chronic complication	1
E12.9	Diabetes without chronic complication	1
E13.0	Diabetes without chronic complication	1
E13.1	Diabetes without chronic complication	1
E13.6	Diabetes without chronic complication	1
E13.8	Diabetes without chronic complication	1
E13.9	Diabetes without chronic complication	1
E14.0	Diabetes without chronic complication	1
E14.1	Diabetes without chronic complication	1
E14.6	Diabetes without chronic complication	1
E14.8	Diabetes without chronic complication	1
E14.9	Diabetes without chronic complication	1
E10.2	Diabetes with chronic complication	2
E10.3	Diabetes with chronic complication	2
E10.4	Diabetes with chronic complication	2
E10.5	Diabetes with chronic complication	2
E10.7	Diabetes with chronic complication	2
E11.2	Diabetes with chronic complication	2
E11.3	Diabetes with chronic complication	2
E11.4	Diabetes with chronic complication	2
E11.5	Diabetes with chronic complication	2
E11.7	Diabetes with chronic complication	2
E12.2	Diabetes with chronic complication	2
E12.3	Diabetes with chronic complication	2
E12.4	Diabetes with chronic complication	2
E12.5	Diabetes with chronic complication	2

ICD-10	Description	Weight
E12.7	Diabetes with chronic complication	2
E13.2	Diabetes with chronic complication	2
E13.3	Diabetes with chronic complication	2
E13.4	Diabetes with chronic complication	2
E13.5	Diabetes with chronic complication	2
E13.7	Diabetes with chronic complication	2
E14.2	Diabetes with chronic complication	2
E14.3	Diabetes with chronic complication	2
E14.4	Diabetes with chronic complication	2
E14.5	Diabetes with chronic complication	2
E14.7	Diabetes with chronic complication	2
G04.1	Hemiplegia or paraplegia	2
G11.4	Hemiplegia or paraplegia	2
G80.1	Hemiplegia or paraplegia	2
G80.2	Hemiplegia or paraplegia	2
G83.0	Hemiplegia or paraplegia	2
G83.1	Hemiplegia or paraplegia	2
G83.2	Hemiplegia or paraplegia	2
G83.3	Hemiplegia or paraplegia	2
G83.9	Hemiplegia or paraplegia	2
I12.0	Renal disease	2
I13.1	Renal disease	2
N03.2	Renal disease	2
N03.3	Renal disease	2
N03.4	Renal disease	2
N03.5	Renal disease	2
N03.6	Renal disease	2
N03.7	Renal disease	2
N05.2	Renal disease	2
N05.3	Renal disease	2
N05.4	Renal disease	2
N05.5	Renal disease	2
N05.6	Renal disease	2
N05.7	Renal disease	2
N25.0	Renal disease	2
Z49.0	Renal disease	2
Z49.1	Renal disease	2
Z49.2	Renal disease	2
Z94.0	Renal disease	2
Z99.2	Renal disease	2
I85.0	Moderate or severe liver disease	2
I85.9	Moderate or severe liver disease	2
I86.4	Moderate or severe liver disease	2
I98.2	Moderate or severe liver disease	2
K70.4	Moderate or severe liver disease	2
K71.1	Moderate or severe liver disease	2

ICD-10	Description	Weight
K72.1	Moderate or severe liver disease	2
K72.9	Moderate or severe liver disease	2
K76.5	Moderate or severe liver disease	2
K76.6	Moderate or severe liver disease	2
K76.7	Moderate or severe liver disease	2
B20.x	AIDS	6
B22.x	AIDS	6
B24.x	AIDS	6

Note: AIDS: acquired immunodeficiency syndrome

Appendix 23. Chapter 6: ICD-10 codes for estimation of hospital frailty risk score

ICD-10 code	Description	Score
F00	Dementia in Alzheimer's disease	7.1
G81	Hemiplegia	4.4
G30	Alzheimer's disease	4
I69	Sequelae of cerebrovascular disease (secondary codes)	3.7
R29	Other symptoms and signs involving the nervous and musculoskeletal systems (R29??6 Tendency to fall)	3.6
N39	Other disorders of urinary system (includes urinary tract infection and urinary incontinence)	3.2
F05	Delirium, not induced by alcohol and other psychoactive substances	3.2
W19	Unspecified fall	3.2
S00	Superficial injury of head	3.2
R31	Unspecified haematuria	3
B96	Other bacterial agents as the cause of diseases classified to other chapters (secondary code)	2.9
R41	Other symptoms and signs involving cognitive functions and awareness	2.7
R26	Abnormalities of gait and mobility	2.6
I67	Other cerebrovascular diseases	2.6
R56	Convulsions, not elsewhere classified	2.6
R40	Somnolence, stupor and coma	2.5
T83	Complications of genitourinary prosthetic devices, implants and grafts	2.4
S06	Intracranial injury	2.4
S42	Fracture of shoulder and upper arm	2.3
E87	Other disorders of fluid, electrolyte and acid- base balance	2.3
M25	Other joint disorders, not elsewhere classified	2.3
E86	Volume depletion	2.3
R54	Senility	2.2
Z50	Care involving use of rehabilitation procedures	2.1
F03	Unspecified dementia	2.1
W18	Other fall on same level	2.1
Z75	Problems related to medical facilities and other health care	2
F01	Vascular dementia	2
S80	Superficial injury of lower leg	2
L03	Cellulitis	2
H54	Blindness and low vision	1.9
E53	Deficiency of other B group vitamins	1.9
Z60	Problems related to social environment	1.8
G20	Parkinson's disease	1.8
R55	Syncope and collapse	1.8
S22	Fracture of rib(s), sternum and thoracic spine	1.8
K59	Other functional intestinal disorders	1.8
N17	Acute renal failure	1.8
L89	Decubitus ulcer	1.7
Z22	Carrier of infectious disease	1.7

ICD-10 code	Description	Score
B95	Streptococcus and staphylococcus as the cause of diseases classified to other chapters	1.7
L97	Ulcer of lower limb, not elsewhere classified	1.6
R44	Other symptoms and signs involving general sensations and perceptions	1.6
K26	Duodenal ulcer	1.6
I95	Hypotension	1.6
N19	Unspecified renal failure	1.6
A41	Other septicaemia	1.6
Z87	Personal history of other diseases and conditions	1.5
J96	Respiratory failure, not elsewhere classified	1.5
X59	Exposure to unspecified factor	1.5
M19	Other arthrosis	1.5
G40	Epilepsy	1.5
M81	Osteoporosis without pathological fracture	1.4
S72	Fracture of femur	1.4
S32	Fracture of lumbar spine and pelvis	1.4
E16	Other disorders of pancreatic internal secretion	1.4
R94	Abnormal results of function studies	1.4
N18	Chronic renal failure	1.4
R33	Retention of urine	1.3
R69	Unknown and unspecified causes of morbidity	1.3
N28	Other disorders of kidney and ureter, not elsewhere classified	1.3
R32	Unspecified urinary incontinence	1.2
G31	Other degenerative diseases of nervous system, not elsewhere classified	1.2
Y95	Nosocomial condition	1.2
S09	Other and unspecified injuries of head	1.2
R45	Symptoms and signs involving emotional state	1.2
G45	Transient cerebral ischaemic attacks and related syndromes	1.2
Z74	Problems related to care-provider dependency	1.1
M79	Other soft tissue disorders, not elsewhere classified	1.1
W06	Fall involving bed	1.1
S01	Open wound of head	1.1
A04	Other bacterial intestinal infections	1.1
A09	Diarrhoea and gastroenteritis of presumed infectious origin	1.1
J18	Pneumonia, organism unspecified	1.1
J69	Pneumonitis due to solids and liquids	1
R47	Speech disturbances, not elsewhere classified	1
E55	Vitamin D deficiency	1
Z93	Artificial opening status	1
R02	Gangrene, not elsewhere classified	1
R63	Symptoms and signs concerning food and fluid intake	0.9
H91	Other hearing loss	0.9
W10	Fall on and from stairs and steps	0.9
W01	Fall on same level from slipping, tripping and stumbling	0.9
E05	Thyrotoxicosis [hyperthyroidism]	0.9

ICD-10 code	Description	Score
M41	Scoliosis	0.9
R13	Dysphagia	0.8
Z99	Dependence on enabling machines and devices	0.8
U80	Agent resistant to penicillin and related antibiotics	0.8
M80	Osteoporosis with pathological fracture	0.8
K92	Other diseases of digestive system	0.8
I63	Cerebral Infarction	0.8
N20	Calculus of kidney and ureter	0.7
F10	Mental and behavioural disorders due to use of alcohol	0.7
Y84	Other medical procedures as the cause of abnormal reaction of the patient	0.7
R00	Abnormalities of heart beat	0.7
J22	Unspecified acute lower respiratory infection	0.7
Z73	Problems related to life-management difficulty	0.6
R79	Other abnormal findings of blood chemistry	0.6
Z91	Personal history of risk-factors, not elsewhere classified	0.5
S51	Open wound of forearm	0.5
F32	Depressive episode	0.5
M48	Spinal stenosis (secondary code only)	0.5
E83	Disorders of mineral metabolism	0.4
M15	Polyarthrosis	0.4
D64	Other anaemias	0.4
L08	Other local infections of skin and subcutaneous tissue	0.4
R11	Nausea and vomiting	0.3
K52	Other noninfective gastroenteritis and colitis	0.3
R50	Fever of unknown origin	0.1

(Note) ?: means any one available character during the term search

Appendix 24. Chapter 6: Tumour characteristics of the study cohort

Factors		Younger age		Older age	
		Surgery (n=33,341)	**PET (n=2,354)**	**Surgery (n=16,096)**	**PET (n=7,013)**
Tumour grade	G1	6788 (20.36%)	137 (5.82%)	2380 (14.79%)	588 (8.38%)
	G2	15908 (47.71%)	346 (14.70%)	7895 (49.05%)	1918 (27.35%)
	G3	5910 (17.73%)	143 (6.07%)	3224 (20.03%)	476 (6.79%)
	GX	1136 (3.41%)	305 (12.96%)	1033 (6.42%)	1921 (27.39%)
	Missing	3599 (10.79%)	1423 (60.45%)	1564 (9.72%)	2110 (30.09%)
NPI	Median (IQR)	3.36 (3.14-4.38)	3.31 (3.1-4.22)	3.6 (3.24-4.5)	3.3 (2.4-3.6)
	I	145 (0.43%)	-	73 (0.45%)	5 (0.07%)
	II	1892 (5.67%)	7 (0.30%)	434 (2.70%)	0 (0.00%)
	III	3575 (10.72%)	10 (0.42%)	1039 (6.46%)	7 (0.10%)
	IV	4324 (12.97%)	14 (0.59%)	2057 (12.78%)	9 (0.13%)
	V	1009 (3.03%)	1 (0.04%)	543 (3.37%)	1 (0.01%)
	Missing	22396 (67.17%)	2322 (98.64%)	11950 (74.24%)	6991 (99.69%)
Her-2 status	Positive	1512 (4.53%)	29 (1.23%)	553 (3.44%)	132 (1.88%)
	Negative	9837 (29.50%)	172 (7.31%)	3970 (24.66%)	945 (13.47%)
	Unknown	21992 (65.96%)	2153 (91.46%)	11573 (71.90%)	5936 (84.64%)
Mortality	All-cause	5,850 (17.55%)	852 (36.19%)	8,654 (53.76%)	6,035 (86.05%)
	Breast-cancer specific	2,970 (8.91%)	590 (25.06%)	2,699 (16.77%)	2,317 (33.04%)

Appendix 25. Chapter 6: Treatments between younger and older women with early-stage breast cancer

Factors	Older (n=23109, 39.3%)	Younger (n=35695, 60.7%)	Total (N=58804)
Initial surgery			
Overall	16,096 (69.65%)	33,341 (93.40%)	49,437 (84.07%)
Breast conserving surgery	1,885 (11.71%)	6,801 (20.40%)	8,686 (17.57%)
Mastectomy	9,419 (58.52%)	19,063 (57.18%)	28,482 (57.61%)
Unknown surgery type	4,792 (29.77%)	7,477 (22.43%)	12,269 (24.82%)
Adjuvant therapy			
Overall	16,031 (69.37%)	33,194 (92.99%)	49,225 (83.71%)
RT alone	33 (0.14%)	147 (0.41%)	140 (0.24%)
CT alone	7 (0.03%)	62 (0.17%)	69 (0.12%)
ET alone	8,522 (36.88%)	9,035 (25.31%)	17,557 (29.86%)
RT+CT	39 (0.17%)	177 (0.50%)	216 (0.37%)
RT+ET	6,514 (28.19%)	14,934 (41.84%)	21,448 (36.47%)
CT+ET	432 (1.87%)	3,030 (8.49%)	3,462 (5.89%)
RT+CT+ET	557 (2.41%)	6,125 (17.16%)	6,682 (11.36%)
Without any adjuvant therapy	65 (0.28%)	147 (0.41%)	212 (0.36%)
Second surgery	1,548 (9.62%)	5,225 (15.67%)	6,773 (13.70%)
Primary endocrine therapy			
Overall	7,013 (30.35%)	2,354 (6.60%)	9,367 (15.93%)
Tamoxifen	2,756 (39.30%)	1,244 (52.85%)	4,000 (42.70%)
Anastrozole	1,392 (19.85%)	569 (24.17%)	1,961 (20.94%)
Letrozole	2,450 (34.94%)	431 (18.31%)	2,881 (30.76%)
Exemestane	50 (0.71%)	36 (1.53%)	86 (0.92%)
Unknown	365 (5.20%)	74 (3.14%)	439 (4.69%)

(Note) IQR: Interquartile range; CT: chemothearpy; RT: radiothreapy; ET: endocrine therapy

Appendix 26. Chapter 6: Survival rates of study cohort and control group adjusted for frailty and comorbidity

Group	Younger			Older		
	5 years	10 years	15 years	5 years	10 years	15 years
Study cohort						
Overall	91.2%	82.0%	71.8%	59.2%	33.3%	16.6%
Surgery	92.6%	83.6%	73.6%	72.7%	45.9%	25.0%
PET	70.7%	60.7%	51.9%	27.0%	8.5%	3.0%
Control group						
Overall	96.2%	90.5%	83.3%	66.3%	39.4%	21.8%

Appendix 27. Chapter 6: Cases of all-cause and breast cancer-specific death for study cohort by treatment and frailty level

	All-cause mortality (N=21,391, 36.38%)				**Breast cancer-specific mortality** (N=8,576, 14.58%)			
	Younger group	**Older group**	**Total**	**P value**	**Younger group**	**Older group**	**Total**	**P value**
Surgery	5,850 (27.35%)	8,654 (40.46%)	14,504 (67.80%)	<0.0001	2,970 (34.63%)	2,699 (31.47%)	5,669 (66.10%)	<0.0001
Non frail	5,650 (26.41%)	7,567 (35.37%)	13,217 (61.79%)	<0.0001	2,904 (33.86%)	2,398 (27.96%)	5,302 (61.82%)	<0.0001
Pre frail	178 (0.83%)	895 (4.18%)	1,073 (5.02%)	<0.0001	59 (0.69%)	251 (2.93%)	310 (3.61%)	<0.0001
Frail	22 (0.10%)	192 (0.90%)	214 (1.00%)	<0.0001	7 (0.08%)	50 (0.58%)	57 (0.66%)	0.1195
PET	852 (3.98%)	6,035 (28.21%)	6,887 (32.20%)	<0.0001	590 (6.88%)	2,317 (27.02%)	2,907 (33.90%)	<0.0001
Non frail	784 (3.67%)	4,151 (19.41%)	4,935 (23.07%)	<0.0001	560 (6.53%)	1,723 (20.09%)	2,283 (26.62%)	<0.0001
Pre frail	51 (0.24%)	1,316 (6.15%)	1,367 (6.39%)	<0.0001	26 (0.30%)	417 (4.86%)	443 (5.17%)	0.3365
Frail	17 (0.08%)	568 (2.66%)	585 (2.73%)	0.0675	4 (0.05%)	177 (2.06%)	181 (2.11%)	0.3152
Total	6,702 (31.33%)	14,689 (68.67%)	21,391 (100.00%)	<0.0001	3,560 (41.51%)	5,016 (58.49%)	8,576 (100.00%)	<0.0001

Appendix 28. Chapter 6: Mean value and standardised mean difference of selected covariates in propensity score before and after balance

Variables	Mean in treat	Mean in untreated	SMD
Age 70-75	0.1	0.1	-0.001
Age 75-80	0.09	0.09	0.000
Age 80-85	0.06	0.06	-0.001
Age 85-90	0.04	0.04	-0.009
Age 90+	0.04	0.04	-0.009
CCI low	0.87	0.87	0.000
CCI intermediate	0.1	0.1	0.002
CCI high	0.03	0.03	-0.003
Non frail	0.92	0.91	0.015
Pre frail	0.06	0.07	-0.008
Frail	0.02	0.02	-0.014
IMD (1-2)	0.23	0.21	0.049
IMD (3-4)	0.19	0.18	0.013
IMD (5-6)	0.16	0.16	-0.006
IMD (7-8)	0.07	0.08	-0.018
IMD (9-10)	0.09	0.11	-0.041

(Note) All variables in propensity score matching were binary variables. SMD: Standardised mean difference; CCI: Charlson Comorbidity Index; IMD: index of multiple deprivation.

Appendix 29. Chapter6: Competing risk regression

For the cohort study, the competing risk regression was undertaken as the sensitivity analysis. Competing risk regression model was the modelling the cause-specific hazard functions via a proportional hazard assumption developed by Fine and Gray (1997) [1]. Since the cause of death for patients with a high level of HFRS and CCI are highly associated with competing events, for example, cardiovascular or cerebrovascular events, competing risk regression analysis allowed analysts to compare the cause-specific hazard of a given event type, which reflects the rate of the event as well as the influence of competing events [2]. Two analytical specifications were performed, (1) competing risk between all-cause death (censoring event) and non-all-cause death (competing event); (2) competing risk between other cause death (censoring event) and breast cancer specific death (competing event). The first specification assessed the result consistency compared with Cox PH regression model; and second specification assess the comparative effectiveness of PET versus surgery by levels of frailty and comorbidity. The subdistribution hazard ratio (SHR) of two model specifications for all covariates was reported, for two treatments (i.e., surgery and PET) by three levels of HFRS and CCI were conducted. Cumulative incidence functions (CIF) for high level of CCI and HFRS were presented to check the time-varying difference for the models.

Result

Similar patterns of results can be seen for the competing risk regression of all selected covariates. For all covariates, in both model 1 and model 2, the SHRs and cumulative incidence increased with the increasing levels of HFRS and CCI (Table A29. 1, Figure A29. 1). For the competing risk of PET compared with surgery by three levels of HFRS and CCI, in both model 1 and model 2, the gap of comparativeness analysis decreased with increasing levels of HFRS and CCI (Table A29. 2). In model 2, for patients at high level of HFRS and CCI, there is no statistical difference of competing risk between other cause death and breast cancer specific death for the patient with PET compared with

those with surgery (Table A29. 2). The SHR was 1.1 (95% CI: 0.9-1.4, p value: 0.261) for patients with high level of HFRS, and the SHR was 1.1 (95% CI: 0.9-1.4, p value: 0.093) for the patients with high level of CCI (Table A29. 2). For patients with high levels of HFRS and CCI in model 1 and model 2, the cumulative incidence between all-cause death and non-all cause death of PET was consistently higher than that of surgery during the analysis time (Figure A29.2).

Table A29.1 Competing risk regression of all selected covariates for cohort study

Factors	Model 1		Model 2	
	SHR (95% CI)	P value	SHR (95% CI)	P value
Age	1.1 (1.1, 1.1)	<0.001	1.1 (1.0, 1.1)	<0.001
Age (time-varying)	1.0 (1.0. 1.0)	0.108	1.0 (1.0. 1.0)	0.335
Treatment (reference surgery)				
PET	1.9 (1.8, 2.0)	<0.001	1.2 (1.1, 1.3)	<0.001
HFRS (reference: non-frail)				
Pre-frail	1.4 (1.3, 1.5)	<0.001	1.3 (1.2, 1.4)	<0.001
Frail	2.0 (1.9, 2.2)	<0.001	1.4 (1.2, 1.6)	<0.001
CCI (reference: low level)				
Intermediate	1.3 (1.3, 1.4)	<0.001	1.3 (1.2, 1.4)	<0.001
High	1.8 (1.7, 1.9)	<0.001	1.6 (1.4, 1.8)	<0.001
IMD (reference: IMD decile 1-2)				
3-4	1.0 (1.0, 1.1)	<0.001	1.1 (1.0, 1.2)	0.095
5-6	1.0 (1.0, 1.1)	<0.001	1.1 (1.0, 1.2)	0.125
7-8	1.1 (1.0, 1.2)	<0.001	1.1 (1.0, 1.2)	0.071
9-10	1.2 (1.1, 1.3)	<0.001	1.1 (1.0, 1.2)	0.001
No observations	1.2 (1.1, 1.3)	<0.001	1.1 (1.0, 1.2)	0.032

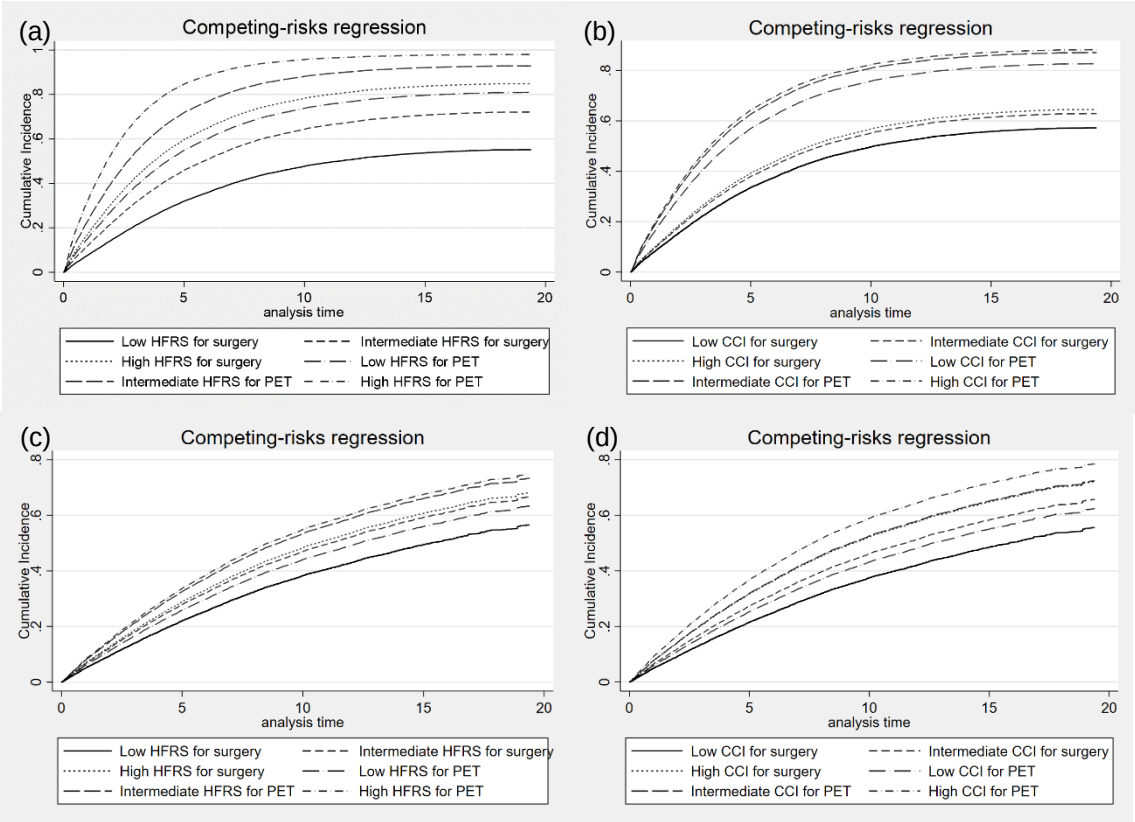
(Note) HR: hazard ratio; SHR: subdistribution hazard ratio; CI: confidence interval; PET: primary endocrine therapy; HFRS: hospital frailty risk score; CCI: Charlson comorbidity index; IMD: index of multiple deprivation; *Model 1 compared the competing risk between all-cause death and non-cause death; Model 2 compared the competing risk between other cause death and breast cancer specific death.

Table A29.2 Competing risk regression of PET compared to surgery by levels of frailty and comorbidity

Group		Model 1		Model 2	
		SHR (95% CI)	P value	SHR (95% CI)	P value
HFRS	Non, frail (0, 5)	2.2 (2.1, 2.3)	<0.0001	1.2 (1.1, 1.3)	<0.0001
	Pre, frail (6, 15)	1.9 (1.7, 2.1)	<0.0001	1.4 (1.2, 1.5)	<0.0001
	Frail (≥15)	1.2 (1.0, 1.4)	0.082	1.1 (0.9, 1.4)	0.261
CCI	Low level of CCI	2.2 (2.1, 2.3)	<0.0001	1.2 (1.1, 1.2)	<0.0001
	Intermediate level of CCI	1.9 (1.7, 2.1)	<0.0001	1.4 (1.2, 1.5)	<0.0001
	High level of CCI	1.4 (1.2, 1.6)	<0.0001	1.1 (0.9, 1.4)	0.093

(Note) HR: hazard ratio; SHR: subdistribution hazard ratio; CI: confidence interval; HFRS: hospital frailty risk score; CCI: Charlson comorbidity index; *Model 1 compared the competing risk between all-cause death and non-cause death; Model 2 compared the competing risk between other cause death and breast cancer specific death.

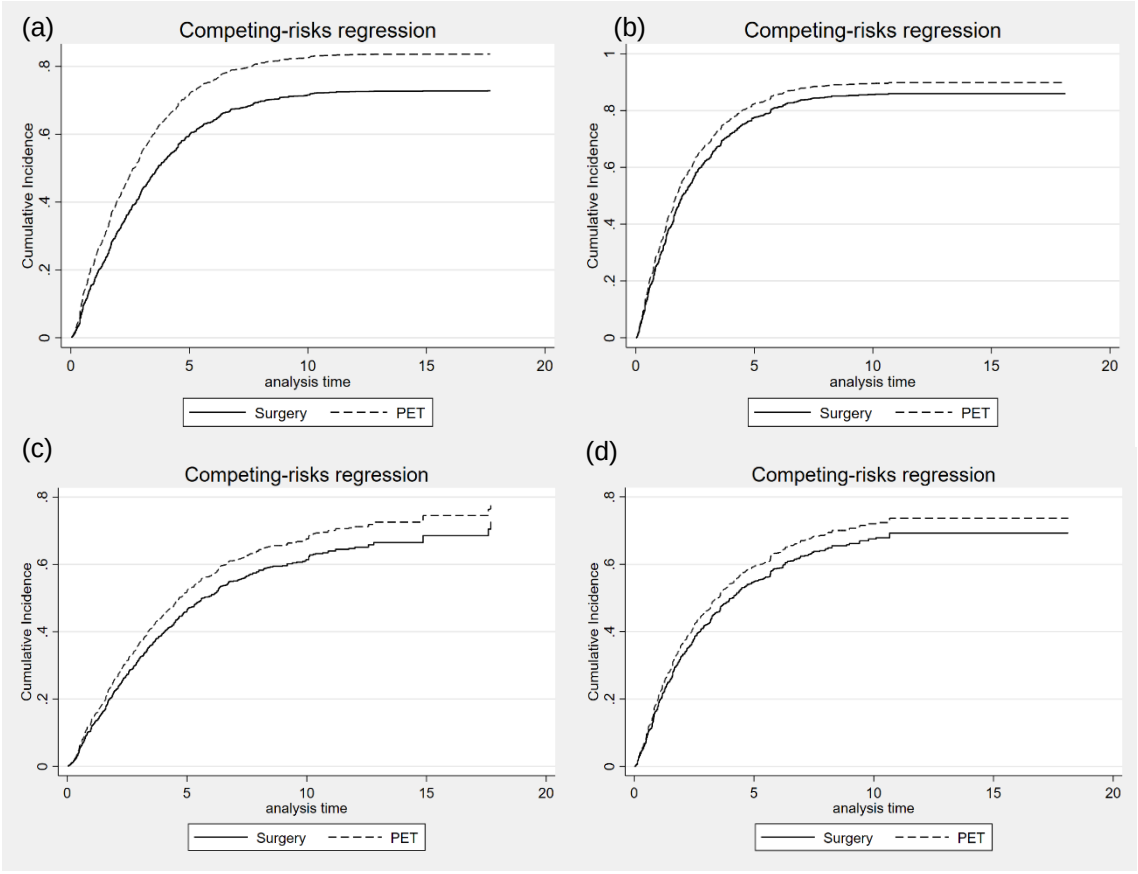
Figure A29.1 Cumulative incidence function of competing risk between PET and surgery in three level of hospital frailty risk scores



(Note) HFRS: hospital frailty risk score; CCI: Charlson comorbidity index. *Model 1 compared the competing risk between all-cause death and non-cause death; Model 2 compared the competing risk between other cause death and breast cancer specific death.

(a) Cumulative incidence function between surgery and PET by three levels of HFRS in Model 1; (b) Cumulative incidence function between surgery and PET by three levels of CCI in Model 1; (c) Cumulative incidence function between surgery and PET by three levels of HFRS in Model 2; (d) Cumulative incidence function between surgery and PET by three levels of CCI in Model 2.

Figure A29.1 Cumulative incidence function of competing risk in high level of frailty between surgery and PET



(Note) *Model 1 compared the competing risk between all-cause death and non-cause death; Model 2 compared the competing risk between other cause death and breast cancer specific death.

(a) Cumulative incidence function with high level of CCI by surgery and PET in Model 1; (b) Cumulative incidence function with high level of HFRS by surgery and PET in Model 1 (c) Cumulative incidence function with high level of CCI by surgery and PET in Model 2; (d) Cumulative incidence function with high level of HFRS by surgery and PET in Model 2.

Reference A29

1. Fine, J.P. and Gray, R.J., *A Proportional Hazards Model for the Subdistribution of a Competing Risk.* Journal of the American statistical association, 1999. **94**(446): p. 496-509.
2. Dignam, J.J., Zhang, Q., and Kocherginsky, M., *The Use and Interpretation of Competing Risks Regression Models.* Clin Cancer Res, 2012. **18**(8): p. 2301-8.

Appendix 30. Chapter 7: CHEERS checklist

Topic	No.	Item	Location where item is reported
Title			
	1	Identify the study as an economic evaluation and specify the interventions being compared.	Title
Abstract			
	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Abstract
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Introduction
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	Methods
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Methods
Setting and location	6	Provide relevant contextual information that may influence findings.	Methods
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Methods
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Methods
Time horizon	9	State the time horizon for the study and why appropriate.	Methods
Discount rate	10	Report the discount rate(s) and reason chosen.	Method
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Methods, Data analysis section
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Methods, Clinical effectiveness section
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Methods, utility section
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Methods, Resource use and cost section
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Methods, Resource use and cost section
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Methods, Model structure & Figure 1

Topic	No.	Item	Location where item is reported
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Methods
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Methods, Clinical effectiveness section
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	Methods, Clinical effectiveness section
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	Methods, Data analysis section
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	Not reported
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Results
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Results, Deterministic base-case analysis
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Results, Sensitivity analyses
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	Results, Value of information analysis & Value of implementation analysis
Discussion			
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Discussion
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Not reported
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Not reported