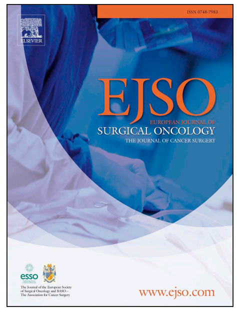
The use of surgery in the treatment of ER+ early stage breast cancer in England: variation by time, age and patient characteristics

RICHARDS, P., WARD, S., MORGAN, J., LAGORD, C., REED, M., COLLINS, K. and WYLD, L.

Published version

RICHARDS, P., WARD, S., MORGAN, J., LAGORD, C., REED, M., COLLINS, K. and WYLD, L. (2016). The use of surgery in the treatment of ER+ early stage breast cancer in England: variation by time, age and patient characteristics. European Journal of Surgical Oncology, 42 (4), 489-496.

Accepted Manuscript



The use of surgery in the treatment of ER+ early stage breast cancer in England: variation by time, age and patient characteristics

Paul Richards, Sue Ward, Jenna Morgan, Catherine Lagord, Malcolm Reed, Karen Collins, Lynda Wyld

PII: S0748-7983(16)00038-X

DOI: 10.1016/j.ejso.2015.12.012

Reference: YEJSO 4222

To appear in: *European Journal of Surgical Oncology*

Received Date: 22 September 2015

Revised Date: 11 December 2015

Accepted Date: 16 December 2015

Please cite this article as: Richards P, Ward S, Morgan J, Lagord C, Reed M, Collins K, Wyld L, The use of surgery in the treatment of ER+ early stage breast cancer in England: variation by time, age and patient characteristics, *European Journal of Surgical Oncology* (2016), doi: 10.1016/j.ejso.2015.12.012.

Title: The use of surgery in the treatment of ER+ early stage breast cancer in England: variation by time, age and patient characteristics

Authors:

Paul Richards[1]

Sue Ward[1]

Jenna Morgan[2]

Catherine Lagord[4]

Malcolm Reed[2]

Karen Collins[3]

Lynda Wyld[2]

Author Affiliations:

1. Department of Health Economics and Decision Science, School for Health and Related Research, University of Sheffield, Sheffield, S1 4DA, UK.

2. Academic Unit of Surgical Oncology, University of Sheffield Medical School, Beech Hill Road, Sheffield, S10 2JF, UK.

3. Centre for Health and Social Care Research, Sheffield Hallam University, Collegiate Crescent, Sheffield, UK.

4. Public Health England, Knowledge and Information Team (West Midlands), Floor 6, 5 St. Philip's Place, Birmingham, B3 2PW, UK.

Corresponding Author:

Paul Richards, Department of Health Economics and Decision Science, School for Health and Related Research, University of Sheffield, Sheffield, UK (p.richards@sheffield.ac.uk)

Conflict of Interest Statement;

The authors declare no conflict of interest.

Abstract:

AIM: To assess whether the proportion of patients aged 70 and over with ER+ operable breast cancer in England who are treated with surgery has changed since 2002, and to determine whether age and individual level factors including tumour characteristics and co-morbidity influence treatment choice.

METHODS: A retrospective cohort analysis of routinely collected cancer registration data from two English regions (West Midlands, Northern & Yorkshire) was carried out (n = 17,129). Trends in surgical use over time for different age groups were assessed graphically and with linear regression. Uni- and multivariable logistic regressions were used to assess the effects of age, comorbidity, deprivation and disease characteristics on treatment choice. Missing data was handled using multiple imputation.

RESULTS: There is no evidence of a change in the proportion of patients treated surgically over time. The multivariable model shows that age remains an important predictor of whether or not a woman with ER+ operable breast cancer receives surgery after covariate adjustment (Odds ratio of surgery vs no surgery, 0.82 (per year over 70)). Co-morbidity, deprivation, symptomatic presentation, later stage at diagnosis and low grade are also associated with increased probability of non-surgical treatment.

CONCLUSION: Contrary to current NICE guidance in England, age appears to be an important factor in the decision to treat operable ER+ breast cancer non-surgically. Further research is needed to assess the role of other age-related factors on treatment choice, and the effect that current practice has on survival and mortality from breast cancer for older women.

Keywords: Breast cancer, elderly, surgery, , comorbidity, retrospective study

Introduction

More than 16,000 women aged 70 or over are diagnosed with breast cancer in the UK each year, accounting for more than 30% of all diagnoses (1). The number of women affected will increase over time due to the ageing population (2). Most older women are diagnosed with oestrogen receptor positive disease (ER+), with estimates ranging from 80-90% (3,4). For postmenopausal women with operable ER+ breast cancer, NICE recommends that usual treatment should consist of surgery with adjuvant endocrine therapy using an aromatase inhibitor, or surgery only if recurrence risk is very low. However, ER+ tumours can respond well to primary endocrine therapy (PET), which consists of sole use of anti-oestrogen therapy without surgery.

The most recent NICE guidelines , issued in 2009, state that PET should only be offered to patients if "significant comorbidity precludes surgery" (page 86), and that age should not affect the decision by itself (5). For patients aged over 70, non-surgical treatment is used in up to 40% of patients, compared with less than 6% in women under 70 (6). There is considerable regional variation in rates of non-surgical treatment within the UK, which is unlikely to be explained solely by population differences or administrative error.

The reason for such high rates of PET usage in older women in unclear. Mortality from breast surgery is very rare in all age groups (7), and where there are concerns over fitness it is often possible to resect the primary tumour under local anaesthetic. In other developed nations such as the USA, Australia, Japan and the Netherlands rates of surgical treatment of breast cancer are higher than in the UK (8) ; for example in the US over 90% of women aged 90 years and over with stage I or II disease are treated surgically (9). As a result it is unlikely that observed rates of non-surgical treatment in the UK are the result of all such patients being too unfit to tolerate surgery.

Historical evidence in support of PET compared with surgical management is derived from several trials run over 20 years ago, which showed no survival advantage for surgery in women over the age of 70 (10). However, in all trials local disease control was observed to be much worse for patients treated with PET compared with surgery, regardless of whether adjuvant endocrine therapy was used. Poor local disease control can result in increased risk of a change in management as well as physical and/or psychological morbidity. None of these trials factored comorbidity or frailty into the analysis, and patients were fit for surgery under general anaesthetic. A recent study has reviewed data from UK cohort studies, which are more likely to reflect actual clinical practice. These studies have shown that surgery may be advantageous for both overall and breast-cancer specific survival (11). The limitations of cohort studies must be recognised. There will be characteristics related to both treatment choice and survival which differ between groups (e.g. frailty, functional status) and this will inevitably lead to higher rates of other cause mortality in the non-surgically treated group. However rates of breast cancer specific survival should be less affected, and these do show some benefit for surgery. A corollary to this is that the high levels of PET use in women aged 70 and over in England may partly explain why relative survival for older women with breast cancer is poor when compared to their contemporaries in other developed nations (12).

Our study aims to analyse UK practice using retrospective cohort study in older women with operable, ER positive breast cancer in order to establish which factors determine selection for surgery or primary endocrine therapy.

Methods

Data on all first diagnoses of invasive breast cancer in women aged 70 and over between the years of 2002 and 2010 were acquired for two UK cancer registry regions (West Midlands, Northern & Yorkshire). Variables provided for analysis are shown in Table 1. Comorbidity was derived from linked records in the Hospital Episode Statistics dataset and aggregated using the Charlson Co-morbidity Index (13) by counting diagnostic codes recorded in episodes in the 18 months prior to diagnosis, an approach used in other studies using routine registration data (14). Deprivation was recorded as quintile of the income domain of the English Indices of Multiple Deprivation 2010 (15), derived from the patient's postcode based on the proportion of households in the local area in receipt of various forms of financial assistance from the state.

Analyses are restricted to the subgroup of patients with operable ER+ disease at diagnosis. Patients with metastatic disease at diagnosis were excluded. It was not possible to identify locally advanced disease definitively due to incomplete staging data, so this criterion may include a small number of tumours which were initially inoperable.

Oestrogen receptor (ER) status is not completely recorded, and in particular was only collected routinely by the Northern & Yorkshire registry from 2009. However, it is known that the completeness of recording of hormone therapy use for these patients was good (6). As a proxy, it was assumed that any patient with unknown ER status but a record of hormone therapy had ER+ disease, as hormone therapy is only effective in these patients. Patients with unknown ER status and no record of hormone therapy were excluded from further analysis. Patients known to have died within 3 months of diagnosis were also excluded, as these patients are likely to have died before planned treatments could commence or will have already had stage 4 disease at the time of diagnosis.

Primary treatment was dichotomised as "surgery" or "no surgery" according to whether the patient had an episode of breast surgery recorded within 6 months of diagnosis (using OPCS4 codesThe proportion of patients treated surgically for each year at diagnosis was plotted for the age subgroups 70-79, 80-89 and 90+. Linear regression using year of diagnosis as the independent variable and controlling for age subgroup was used to investigate evidence of temporal trends in treatment. Graphical methods were used to display the associations between age, deprivation and treatment. Simple logistic regression was used to identify associations between covariates with complete data and treatment choice. The joint effect of selected patient level factors (age, deprivation, comorbidity, method of detection, tumour diameter, nodal status, tumour grade) on the probability of surgical treatment was assessed using multivariable logistic regression.

Some covariates contain missing values. The "gold standard" for tumour characteristics and staging data is to derive them from pathology reports, but such information will be incomplete if surgery is omitted and may sometimes be missing for surgically treated patients as well.

Although values may be recorded on the basis of other information (biopsy, imaging, etc.), in some cases no value is available. Analyses based on case-wise deletion of individuals with missing values can lead to biased results due to selection bias if data is not missing completely at random, and also results in a loss of statistical precision. Missing data on disease characteristics and comorbidity was handled as suggested by Nur *et al* (16), using the method of multiple imputation by chained equations (MICE) (17). This method involves imputing missing values multiple times, conditional on the other values observed in the dataset. Twenty-five completed datasets were used for the multivariable analyses only. As the imputation method draws on information from many covariates, this method was not used to estimate associations between individual variables with incomplete data and treatment choice; doing so can result in incorrect estimates for standard errors (18) .Results from the 25 multivariable regression models fitted to each of the imputed datasets were combined using methods described by Rubin (19). Covariates with over 50% missing data were not included in the base-case regression models. Numeric stage was included in the imputations but omitted from the regressions in favour of tumour size and nodal status. This decision was taken because numeric stage is closely correlated with these variables by definition, and so including it would make identification of the effect of tumour size and node positivity difficult.

The ability of the regression model to predict whether a patient would be treated surgically was assessed by calculating the ROC curve and its corresponding area under the curve (AUC) statistic (20). All analyses were conducted using the open source statistical programming language R (version 3.0.1) (21). The user-contributed CRAN packages “mi” (22)and “pROC” (23) were used to implement the MICE algorithm and the ROC analyses respectively.

Results

The dataset contained records on 23,960 diagnoses of primary breast cancer. After applying the exclusion criteria described in the previous section, a total of 17,129 records remained for analysis (Fig 1). On the basis of the assumptions made to define ER status, it was estimated that 77% of this group had ER+ tumours. This is in line with audit data for England which shows that between 78 and 80% of women in this age group present with ER+ disease.

Patient characteristics are shown in Table 1. Missing data is more prevalent in patients who are treated non-surgically. In particular, information on nodal status is only recorded for 9% of patients treated non-surgically compared with 84% of patients treated surgically. This finding has been noted in previous audits of cancer registration data, and is unsurprising since tumour size and nodal status is most accurately assessed from post-operative pathology based on the resected tumour and lymph nodes. Regardless of treatment, the rates of missing data for most incomplete covariates increase with age.

There was no evidence of a trend in the proportion of patients receiving surgical treatment between 2002 and 2010 regardless of age at diagnosis (Fig 2). The modelled increase in the proportion surgically treated per year was 0.00 for age 70-79 ($p = 0.39$), 0.00 for age 80-89 ($p = 0.33$) and 0.00 for age 90+. As a sensitivity analysis the proportions were also calculated for the whole dataset regardless of stage at diagnosis and ER status, but again no trends were observed (data not shown).

The univariable regressions show that increased age at diagnosis, high deprivation and symptomatic presentation are all strongly associated with non-surgical treatment, without accounting for the effects of other variables (Table 2). The negative association between the probability of surgical treatment and age at diagnosis can be seen in Figure 3. The proportion receiving surgery declines from 91.1% at age 70 to 38.5% at age 85 and less than 3% at age 95 and over. Between the ages of 70 and 85 deprivation is associated with non-surgical treatment. The observed proportion of surgical treatment is greater in the least deprived quintile compared with the most deprived quintile at all ages in this range, with the absolute increase associated with low deprivation ranging from between 4% (at age 79) and 25% (at age 78).For women aged over 85, no association with deprivation is observed. Although presentation at screening is strongly associated with surgery, screening was not routinely offered to this population (24) and these women are most likely self-referrals.

The multivariable logistic regression model after combining results from the imputed datasets is shown in Table 3. HER2 status was not included due to the majority of data being missing. Exploratory analysis of the imputed datasets did not raise major concerns about the plausibility of the imputed values (data not shown), although by definition any discrepancies cannot be measured.

All variables assessed in the final model are significantly associated with treatment type. Older age, symptomatic presentation, increased Charlson score, high income deprivation, lymph node involvement, larger tumour size and grade 1 or 2 disease are associated with a higher probability of non-surgical treatment. The ROC curve for the logistic model is presented in Figure 4, as well as for a decision rule based on using age at diagnosis alone to predict treatment. The area under the model curve (AUC) is 0.848 (95% CI, 0.843 – 0.854), indicating that the model discriminates well between patients treated surgically and non-surgically. The regression model provides a modest improvement over using age as the sole predictor, which has AUC = 0.807 (95% CI, 0.801 – 0.814). This shows that age at diagnosis accounts for much of the variability in treatment decision making in this population.

Discussion

This analysis suggests that age is the single most important factor associated with non-surgical treatment of older breast cancer patients with operable ER+ disease in England. The finding persists when income deprivation, co-morbidities and disease characteristics are accounted for, although the multivariable model shows that these factors do predict treatment to a lesser extent. There is no evidence of a change in the rate of surgical treatment over time. The model discriminates well between patients treated surgically and non-surgically, but there is residual variability in treatment decisions not explained by this data. There is also a suggestion that socio-economic factors have an independent effect on treatment choice, with increased income deprivation being predictive of non-surgical treatment for patients aged 70-85. Overall, the results of this model suggest that NICE guidance for the use of PET is not being adhered to consistently.

Our results are largely consistent with those of other UK cohort studies (25–28). In particular, in a previous analysis of cancer registration data on diagnoses between the years of 1997 and 2005, Lavelle *et al* found that age remains a significant predictor of treatment after controlling for comorbidity (26). Our analysis builds on this previous work in a number of ways. Firstly, inclusion of diagnoses up to and including 2010 means that it is more reflective of contemporary practice. In recent years completeness of cancer registration data has improved, so the findings of this analysis should be less prone to missing data bias (6). Our study considers the joint impact of all variables by accounting for missing data using multiple imputation. This method is less prone to bias than other approaches to analysing registry data such as complete case analysis or treating “missing” as a category in a factor variable (16). There is, however, no perfect method for accounting for missing data and by definition results cannot be verified from the data alone. Our multivariable analysis demonstrates that age is highly predictive of non-surgical treatment, and that comorbidity, deprivation and disease characteristics also contribute to this treatment decision. This conclusion from the analysis is possible despite this missing data, but if the relationship between disease characteristics and other factors differs significantly between the PET and surgery groups there will be some bias in estimates of the regression coefficients for these characteristics.

Our data shows no evidence of any trend in the use of surgery in the West Midlands and Northern & Yorkshire regions between 2002-10. This contrasts with emerging evidence from the Netherlands which shows a marked decrease in the use of surgery in this population over the same period, though rates remain considerably higher than in the UK (29). Interestingly, overall and relative survival at 5 years remained almost unchanged in the Netherlands over this time period. This suggests that non-surgical treatment can result in good outcomes, provided it is targeted effectively, though care must be taken when comparing data from different countries due to differences in demographics and health systems.

Our methods have a number of limitations. It is known that the prevalence of chronic conditions increases with age, and older people are more likely to be diagnosed with multiple such conditions (multimorbidity) (30). The HES based method used to measure comorbidity may underestimate the true burden of comorbidity in the elderly. This method has been adopted as standard in other analyses of cancer registration data (14,26), which have found that the resultant measure is positively correlated with negative outcomes. However, the proportion of patients recorded as having one or more comorbid condition in the dataset is considerably lower than estimates for US breast cancer patients (9) and in the general UK population (30) in this age range. This may be because some chronic conditions in the elderly are primarily controlled in a non-inpatient setting and are therefore not identified in in-patient and day case HES data. This also explains the higher rate of missing values within the "no surgery" arm. Future developments in health care data linkage may allow for more accurate identification of comorbidities using routine data sources, which in turn would allow for a more in depth understanding about the relationship this plays with choices about breast cancer therapy In addition, it is not clear that the Charlson index is the most appropriate method of aggregating comorbidity in this study, as it was originally developed and validated as a prognostic index for mortality and is not elderly-specific (13).

Multimorbidity alone does not fully describe age-related heterogeneity in health (31), and other measures such as functional status and cognitive function are known to be age dependent (32). These factors do not necessarily correlate with comorbidity in an elderly population (33) and are missing from our dataset. Poor functional status has been observed to be predictive of non-surgical treatment in other prospective cohort studies (27). Omission of surgery may be reasonable given such patients may be more prone to adverse outcomes after surgery and be at greater risk of loss of independence due to frailty. However the potential effect on survival outcomes must not be ignored when making treatment decisions.

The impact of patient choice on treatment decisions is not recorded in registry data. Patient choice may partly reflect the preference of the clinician (34). Qualitative research has shown that older breast cancer patients were largely passive in making treatment decisions and deferred choice to the staff responsible for their care (35). A recent study has shown that where patients perceive that their role in treatment decision making was not discussed, they were more likely to be treated non-surgically (27). Interestingly, the authors found that for 46% (123/267) of patients who felt this way, the responsible clinician believed that the patient took an active or collaborative role in choosing treatment. This suggests that high rates of PET are very unlikely to be solely due to patients actively opting out of surgery, and that there is scope for improving patient involvement in treatment decision making.

In summary, this study has found that age remains animportant factor in the use of non-surgical treatment in older women with ER+ operable breast cancer, even after adjusting for disease characteristics, co-morbidity and deprivation. Although not all relevant factors can be assessed using cancer registration data, the resulting model discriminates well between patients treated surgically and non-surgically. Further research is ongoing to assess the effect that treatment with PET has on survival, which in time will hopefully allow for more evidence based guidelines to be developed for this growing population.

Acknowledgments:

The authors would like to thank Gill Lawrence and Matthew Francis from Public Health England Knowledge and Information Team (West Midlands) and Sarah Lawton from Public Health England Knowledge and Information Team (Northern & Yorkshire) for their help with data collection and processing.

Funding Source:

National Institute for Health Research.

Role of the Funding Source:

This article presents independent research funded by the National Institute for Health Research (NIHR) under the Programme Grants for Applied Research programme (RP-PG-1209-10071). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

REFERENCES

1. Cancer Research UK. Breast cancer incidence statistics [Internet]. 2014. Available from: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/breast/incidence/uk-breast-cancer-incidence-statistics#age

2. Alberg AJ, Singh S. Epidemiology of breast cancer in older women: implications for future healthcare. Drugs Aging [Internet]. 2001 Jan [cited 2014 Jul 10];18(10):761–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11735623

3. Diab SG, Elledge RM, Clark GM. Tumor characteristics and clinical outcome of elderly women with breast cancer. J Natl Cancer Inst [Internet]. 2000 Apr 5 [cited 2011 Oct 5];92(7):550–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10749910

4. Lawrence G, Kearins O, Lagord C, Cheung S, Sidhu J, Sagar C. The Second All Breast Cancer Report [Internet]. London; 2011. Available from: http://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0CCMQFjAA&url=http://www.ncin.org.uk/view.aspx?rid=612&ei=sXd1UMOxPLSM0wWV5YGQDA&usg=AFQjCNFnTgxV6RFCyNAmP4hKZ2wpdX639A

5. National Institute of Clinical Excellence. Early and locally advanced breast cancer: diagnosis and treatment. London; 2009.

6. BCCOM. Breast Cancer Clinical Outcome Measures (BCCOM) Project. Birmingham, UK; 2007.

7. Reed MWR, Audisio RA, Wyld L. The role of surgery in the treatment of older women with breast cancer. Clin Oncol (R Coll Radiol) [Internet]. 2009 Mar [cited 2010 Oct 31];21(2):103–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19073360

8. Wyld L, Hind D. Primary Endocrine Therapy for the Treatment of Breast Cancer in Older Women. In: Reed M, Audisio RA, editors. Management of Breast Cancer in Older Women. First. London: Springer-Verlag; 2010. p. 143–64.

9. Schonberg MA, Marcantonio ER, Li D, Silliman RA, Ngo L, McCarthy EP. Breast

cancer among the oldest old: tumor characteristics, treatment choices, and survival. J Clin Oncol [Internet]. 2010 Apr 20 [cited 2011 Sep 8];28(12):2038–45. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2860406&tool=pmcentrez&rendertype=abstract

10. Morgan J, Wyld L, Collins KA, Reed MW. Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus). Cochrane database Syst Rev [Internet]. 2014 May 16 [cited 2014 May 24];5:CD004272. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24838672

11. Morgan J, Reed MW, Wyld L. Primary endocrine therapy as a treatment for older women with operable breast cancer - a comparison of randomised controlled trial and cohort study findings. Eur J Surg Oncol [Internet]. Elsevier; 2014 Jun 6 [cited 2014 Jun 26];40(6):676–84. Available from: http://www.ejso.com/article/S0748798314003023/fulltext

12. Walters S, Maringe C, Butler J, Rachet B, Barrett-Lee P, Bergh J, et al. Breast cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK, 2000-2007: a population-based study. Br J Cancer [Internet]. Cancer Research UK; 2013 Mar 19 [cited 2014 May 25];108(5):1195–208. Available from: http://dx.doi.org/10.1038/bjc.2013.6

13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis [Internet]. 1987 Jan [cited 2011 Jul 19];40(5):373–83. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3558716

14. Morris EJA, Taylor EF, Thomas JD, Quirke P, Finan PJ, Coleman MP, et al. Thirty-day postoperative mortality after colorectal cancer surgery in England. Gut [Internet]. 2011 Jun 12 [cited 2014 Jul 4];60(6):806–13. Available from: http://gut.bmj.com/content/early/2011/03/08/gut.2010.232181.abstract

15. Department for Communities and Local Government. English indices of deprivation 2010 [Internet]. London, UK.; 2010. Available from: https://www.gov.uk/government/publications/english-indices-of-deprivation-2010

16. Nur U, Shack LG, Rachet B, Carpenter JR, Coleman MP. Modelling relative survival in the presence of incomplete data: a tutorial. Int J Epidemiol [Internet]. 2010 Feb [cited 2013 Aug 12];39(1):118–28. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/19858106

17. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med [Internet]. 2011 Mar 20 [cited 2014 May 30];30(4):377–99. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21225900

18. Meng X-L. Multiple-Imputation Inferences with Uncongenial Sources of Input. Stat Sci [Internet]. Institute of Mathematical Statistics; 1994 Nov 1 [cited 2015 Dec 10];9(4):538–58. Available from: http://projecteuclid.org/euclid.ss/1177010269

19. Rubin DB. Multiple Imputation for Nonresponse in Surveys [Internet]. Wiley-Blackwell; 1987 [cited 2014 Jul 4]. 320 p. Available from: http://www.amazon.co.uk/Multiple-Imputation-Nonresponse-Surveys-Classics/dp/0471655740

20. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology [Internet]. 1982 Apr [cited 2014 May 30];143(1):29–36. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7063747

21. R Core Team. R: A Language and Environment for Statistical Computing [Internet]. Vienna, Austria; 2014. Available from: http://www.r-project.org

22. Su Y-S, Gelman A, Hill J, Yajima M. Multiple Imputation with Diagnostics ({mi}) in {R}: Opening Windows into the Black Box. J Stat Softw [Internet]. 2011;45(2):1–31. Available from: http://www.jstatsoft.org/v45/i02/

23. Robin X, Turck N, Hainard A, Tiberti N, Lisacek F, Sanchez J-C, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. BMC Bioinformatics [Internet]. 2011 Jan [cited 2014 May 23];12(1):77. Available from: http://www.biomedcentral.com/1471-2105/12/77

24. National Health Service. NHS Breast Screening Programme Annual Review 2012. Sheffield, UK; 2012.

25. Wyld L, Garg DK, Kumar ID, Brown H, Reed MWR. Stage and treatment variation with age in postmenopausal women with breast cancer: compliance with guidelines. Br J Cancer [Internet]. 2004 Apr 19 [cited 2011 Sep 29];90(8):1486–

91. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2409727&tool=pmcentrez&rendertype=abstract

26. Lavelle K, Downing A, Thomas J, Lawrence G, Forman D, Oliver SE. Are lower rates of surgery amongst older women with breast cancer in the UK explained by co-morbidity? Br J Cancer [Internet]. 2012 Sep 25 [cited 2012 Oct 10];107(7):1175–80. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3461147&tool=pmcentrez&rendertype=abstract

27. Lavelle K, Sowerbutts AM, Bundred N, Pilling M, Degner L, Stockton C, et al. Is lack of surgery for older breast cancer patients in the UK explained by patient choice or poor health? A prospective cohort study. Br J Cancer [Internet]. Cancer Research UK; 2014 Feb 4 [cited 2014 Jul 4];110(3):573–83. Available from: http://dx.doi.org/10.1038/bjc.2013.734

28. Bates T, Evans T, Lagord C, Monypenny I, Kearins O, Lawrence G. A population based study of variations in operation rates for breast cancer, of comorbidity and prognosis at diagnosis: Failure to operate for early breast cancer in older women. Eur J Surg Oncol [Internet]. 2014 Oct [cited 2014 Oct 23];40(10):1230–6. Available from: http://www.sciencedirect.com/science/article/pii/S0748798314004715

29. de Glas NA, Jonker JM, Bastiaannet E, de Craen AJM, van de Velde CJH, Siesling S, et al. Impact of omission of surgery on survival of older patients with breast cancer. Br J Surg [Internet]. 2014 Oct [cited 2015 Dec 10];101(11):1397–404. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25088709

30. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet [Internet]. 2012 Jul 7 [cited 2012 Jul 14];380(9836):37–43. Available from: http://dx.doi.org/10.1016/S0140-6736(12)60240-2

31. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J Gerontol A Biol Sci Med Sci [Internet]. 2004 Mar;59(3):255–63. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15031310

32. Gosney MA. Clinical assessment of elderly people with cancer. Lancet Oncol [Internet]. 2005 Oct [cited 2011 Oct 7];6(10):790–7. Available from: http://dx.doi.org/10.1016/S1470-2045(05)70389-2

33. Extermann M, Overcash J, Lyman GH, Parr J, Balducci L. Comorbidity and functional status are independent in older cancer patients. J Clin Oncol [Internet]. 1998 Apr [cited 2012 Oct 10];16(4):1582–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9552069

34. Hamaker ME, Bastiaannet E, Evers D, Water W van de, Smorenburg CH, Maartense E, et al. Omission of surgery in elderly patients with early stage breast cancer. Eur J Cancer [Internet]. 2012 Sep 6 [cited 2012 Sep 11];null(null). Available from: http://dx.doi.org/10.1016/j.ejca.2012.08.010

35. Husain LS, Collins K, Reed M, Wyld L. Choices in cancer treatment: a qualitative study of the older women's (>70 years) perspective. Psychooncology [Internet]. 2008 Apr [cited 2011 Aug 4];17(4):410–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17847124

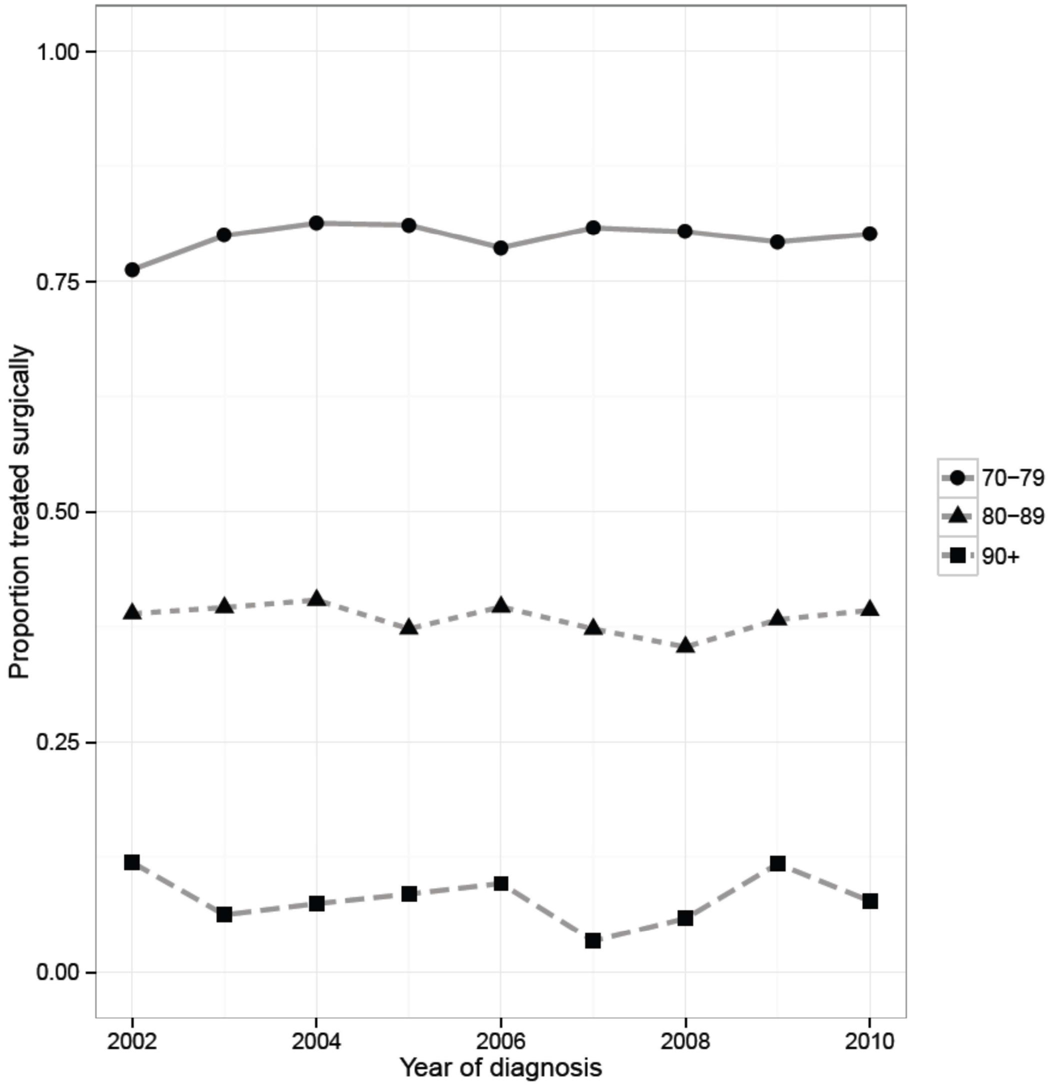


Figure 2: Proportion of patients treated surgically over time, split by 10 year age bands for age at diagnosis

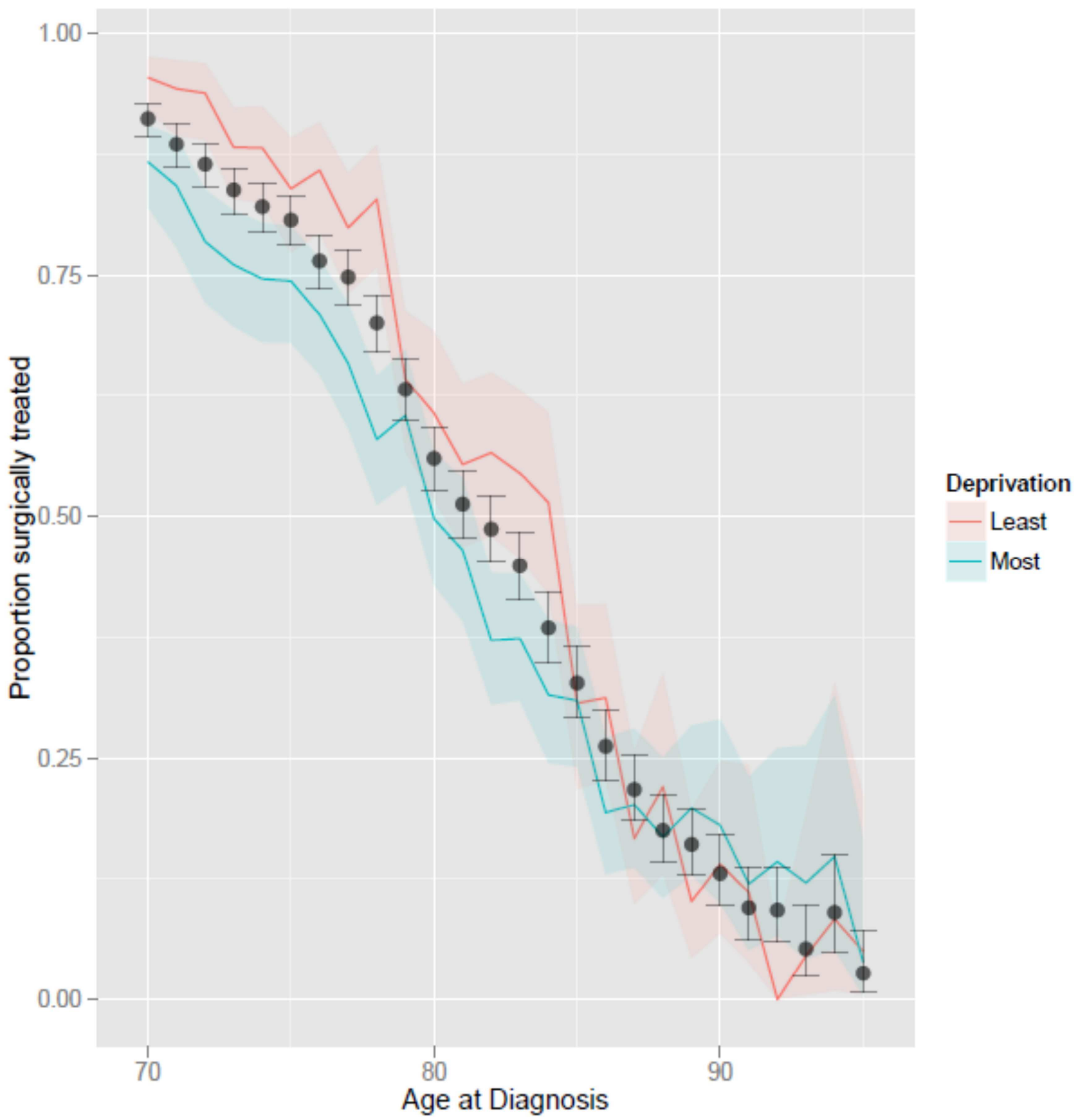


Figure 3: Proportion of ER+ patients with early breast cancer treated with surgery by age at diagnosis, for the whole population (points) and within the top and bottom quintiles of deprivation. Bars and ribbons indicate 95% confidence intervals

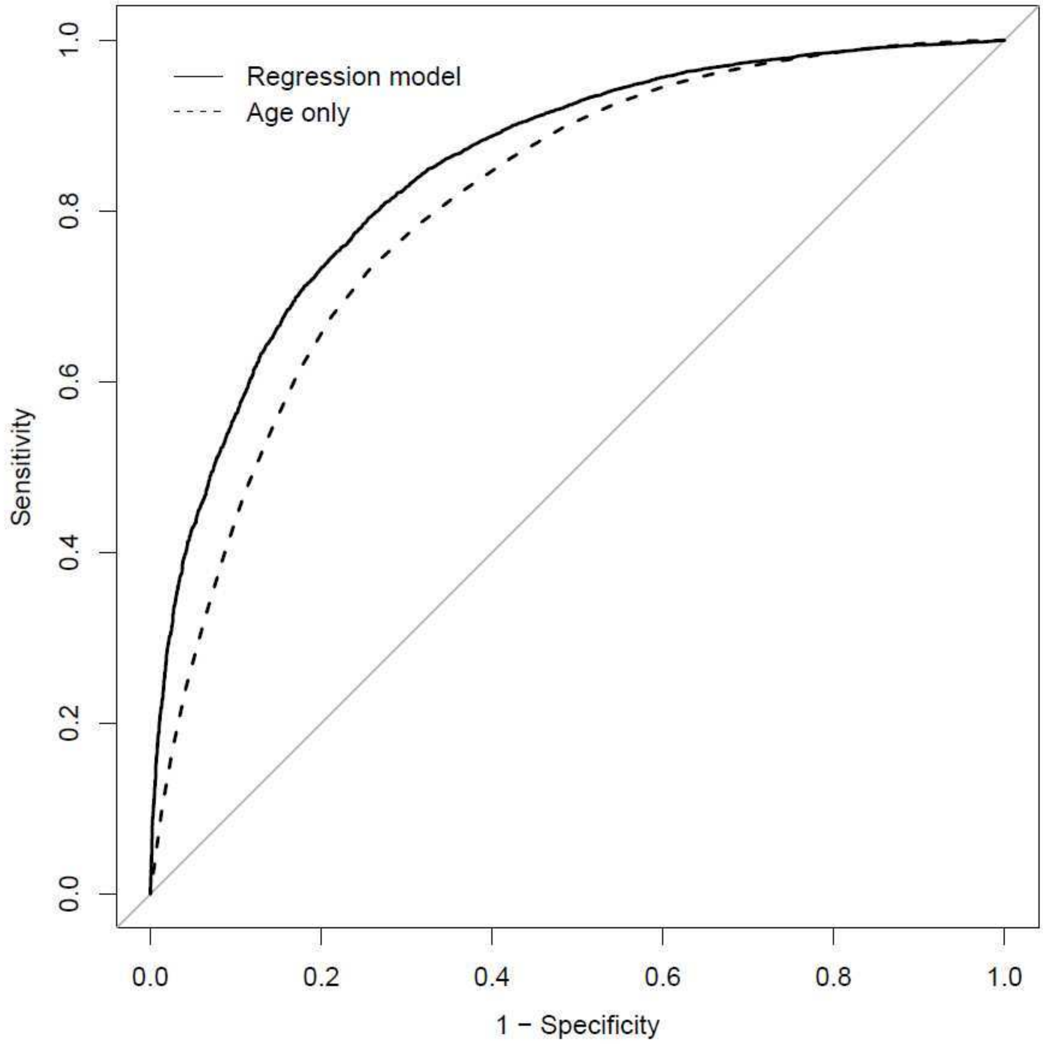


Figure 4: Receiver-operator characteristic (ROC) curves for the predictions from the multivariable logistic regression model, and using age as a sole predictor

Table 1: Patient characteristics

Patient and tumour characteristics		Prevalence (%)	Number who underwent surgery	Rate of surgical treatment
		17129	9955	58.1%
Age at diagnosis (years)				
	70-74	4576 (27)	3958	86.5%
	75-79	4582 (27)	3349	73.1%
	80-84	3960 (23)	1913	48.3%
	85-89	2645 (15)	625	23.6%
	90-94	1053 (6)	104	9.9%
	95+	313 (2)	6	1.9%
	Mean	79.6 years	76.6 years	
Deprivation Quintile				
	1 (least deprived)	2785 (16)	1800	64.6%
	2	3540 (21)	2178	61.5%
	3	3390 (20)	2012	59.4%
	4	3636 (21)	1977	54.4%
	5 (most deprived)	3779 (22)	1989	52.6%
Comorbidity (HES proxy Charlson)				
	0	12160 (71)	8719	71.7%
	1	1253 (7)	588	46.9%
	2	629 (4)	279	44.4%
	>2	337 (2)	77	22.9%
	Missing	2750 (16)	292	10.6%
Method of detection				
	Symptomatic	16014 (93)	8888	55.5%
	Screening	1115 (7)	1067	95.7%
Tumour Size at Diagnosis (diameter, mm, invasive component)				
	(<10)	762 (4)	680	89.2%
	(10-20)	3702 (22)	3154	85.2%
	(20-50)	6465 (38)	4844	74.9%
	(>50)	862 (5)	555	64.4%
	Missing	5338 (31)	722	13.5%
Nodal Status				
	Negative	5107 (30)	4847	94.9%
	Positive	3881 (23)	3480	89.7%
	Missing	8141 (47)	1628	20.0%
TNM Stage				
	I	4215 (25)	3412	80.9%

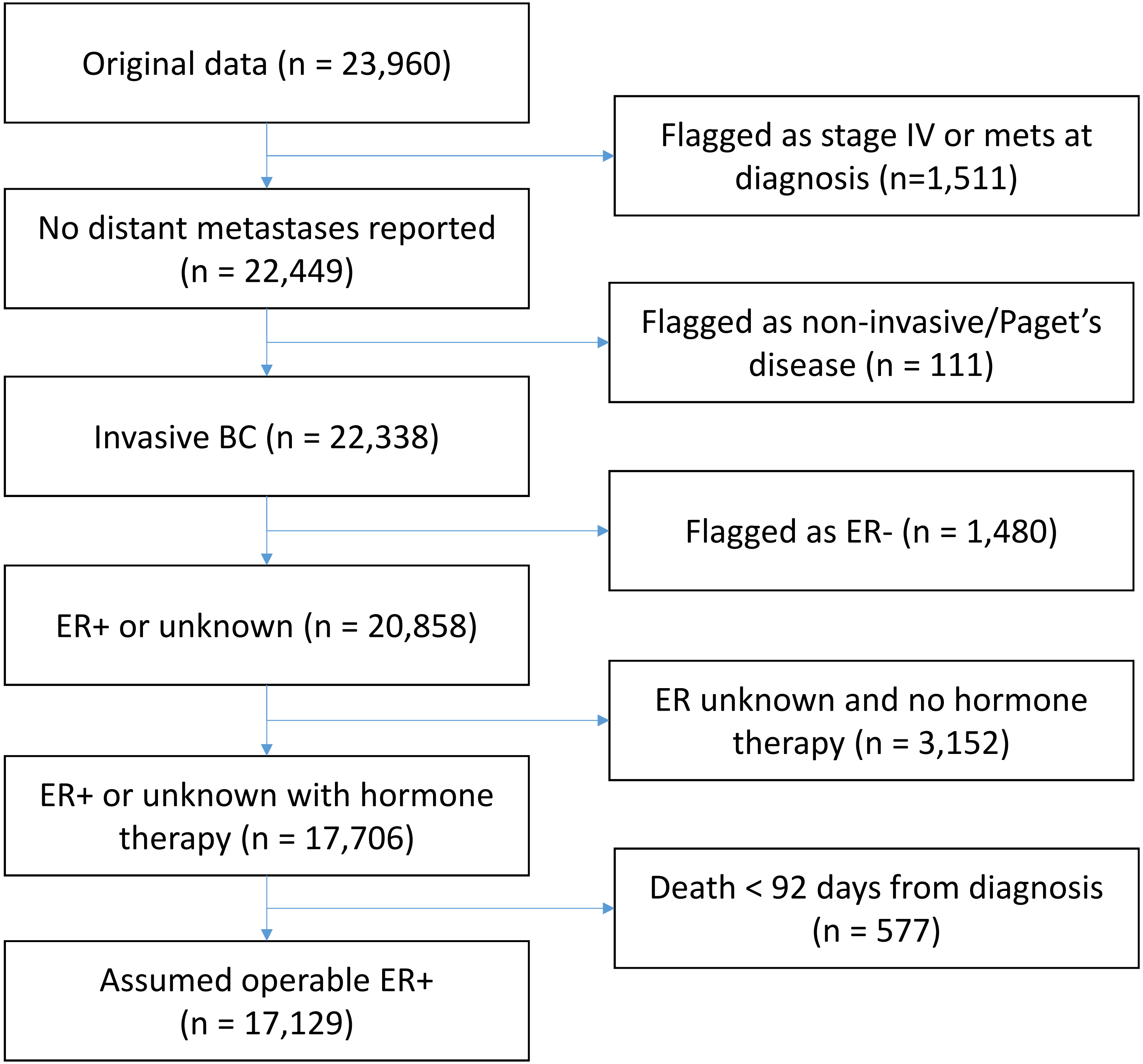
	II	6617 (38)	5097	77.0%
	III	1295 (7)	877	67.7%
	Missing	5002 (29)	569	11.4%
Bloom Richardson Grade				
	1	2720 (16)	1783	65.6%
	2	8567 (50)	5516	64.4%
	3	3200 (19)	2385	74.5%
	Missing	2642 (15)	271	10.3%
HER2 Status				
	Negative	3821 (22)	2824	73.9%
	Positive	514 (3)	367	71.4%
	Missing	12794 (75)	6764	52.9%

Table 2: Odds ratios of complete covariates on surgical treatment, calculated using uni-variable logistic regression. Values < 1 indicate reduced probability of surgical treatment (* indicates p-value for trend)

		Odds Ratio (surgery vs no surgery)	95% confidence interval	P
Age at diagnosis	(per year over 70)	0.81	(0.80, 0.81)	<0.001
Deprivation Qunitile	1 (least)	Reference	-	<0.001*
	2	0.86	(0.79, 0.97)	
	3	0.80	(0.72, 0.89)	
	4	0.65	(0.59, 0.72)	
	5 (most)	0.61	(0.55, 0.67)	
Detection Route	Screened	Reference	-	
	Symptomatic	0.056	0.042	<0.001

Table 3: Multivariable logistic regression of the probability of surgical treatment given individual level characteristics (* indicates p-value for trend)

		Odds Ratio (surgery vs. no surgery)	Lower 95% limit	P - value
Age at diagnosis	(per year over 70)	0.82	(0.81, 0.82)	<0.001
Charlson Index	(per unit increase)	0.53	(0.50, 0.56)	<0.001
Deprivation	1 (least)	Reference	-	<0.001*
	2	0.88	(0.77, 1.00)	
	3	0.83	(0.73, 0.95)	
	4	0.69	(0.61, 0.78)	
	5 (most)	0.61	(0.54, 0.69)	
Detection Route	Screened	Reference	-	<0.001
	Symptomatic	0.34	(0.25, 0.47)	
Bloom-Richardson Grade	1	Reference	-	<0.001*
	2	1.10	(0.98, 1.23)	
	3	1.82	(1.58, 2.11)	
Nodal Status	Negative	Reference	-	0.015
	Positive	0.85	(0.74, 0.97)	
Tumour Size	(per mm increase in diameter)	0.982	(0.979, 0.985)	<0.001


Original data (n = 23,960)
Flagged as stage IV or mets at diagnosis (n=1,511)
No distant metastases reported (n = 22,449)
Flagged as non-invasive/Paget’s disease (n = 111)
Invasive BC (n = 22,338)
Flagged as ER- (n = 1,480)
ER+ or unknown (n = 20,858)
ER unknown and no hormone therapy (n = 3,152)
ER+ or unknown with hormone therapy (n = 17,706)
Death < 92 days from diagnosis (n = 577)
Assumed operable ER+ (n = 17,129)