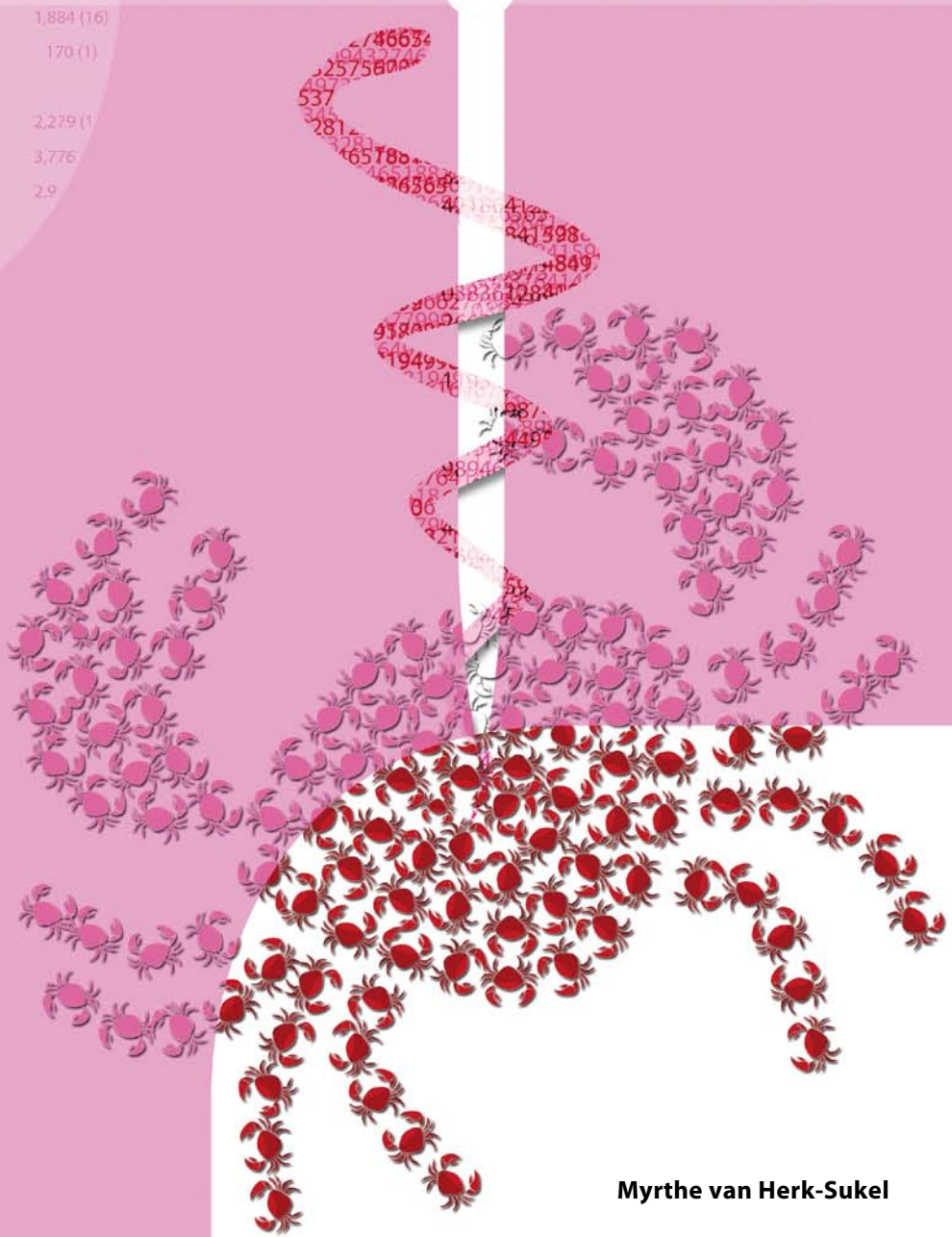
Medication Use Among Women With Breast Cancer in the Netherlands

Pharmacoepidemiological studies based on data from the Eindhoven Cancer Registry-PHARMO linkage



Myrthe van Herk-Sukel

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The research presented in this thesis was performed at the PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands, in close cooperation with the Comprehensive Cancer Centre South [Integraal Kankercentrum Zuid], Eindhoven, The Netherlands.

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van de IKZ-PHARMO koppeling

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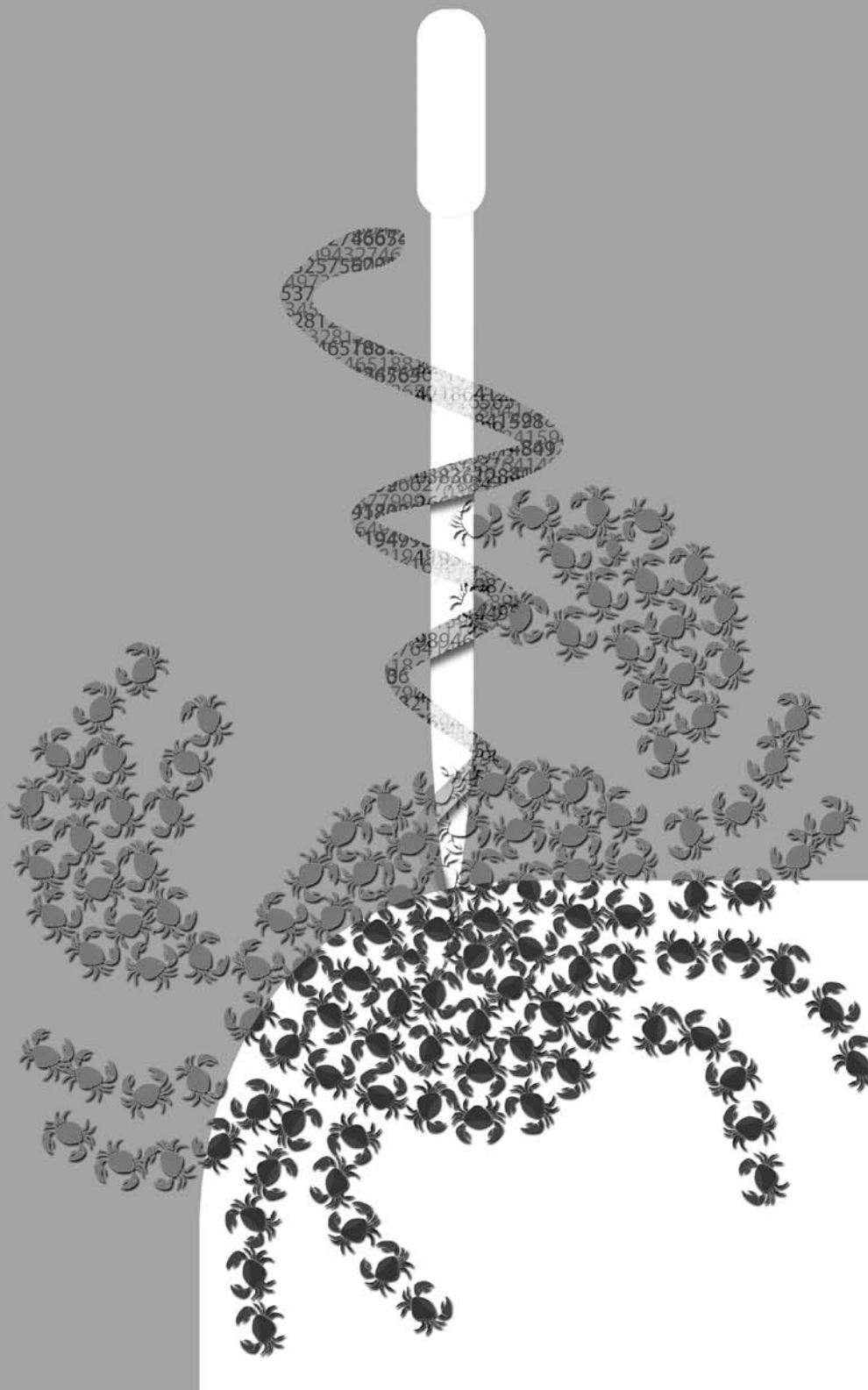
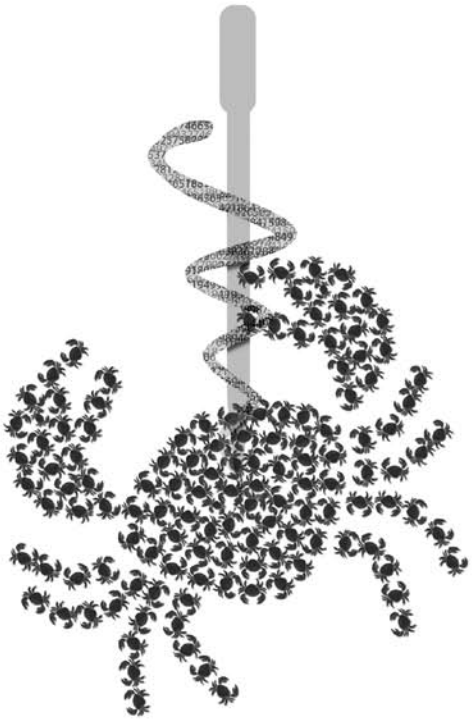
CONTENTS



CHAPTER 1 INTRODUCTION

1.1 Background



Breast cancer epidemiology

In the Netherlands, breast cancer is the most frequent (30%) of all cancers in women[1]. In 2008, around 13,000 women were newly diagnosed with the disease[1]. Worldwide, breast cancer accounted for almost 1.4 million new cancer patients in 2008[2].

Incidence rates of breast cancer have been increasing in the Netherlands since 1960[3]. This increase can be explained by several factors: the increased detection of (early) breast cancer due to the introduction and increased use of mammography and cytology since the 1980s, the implementation of the mass breast cancer screening program between 1991 and 1996, and a change in adverse way of the risk factors for breast cancer over the years. Many known risk factors are related to endogenous hormones: young age at menarche, higher age at menopause, high age at first childbirth, lower parity, shorter lactation and obesity[4]. Changes in adverse way of these reproductive patterns and other lifestyle factors, such as physical activity[5], have almost certainly played an important role in the increase of breast cancer incidence.

In 2008, 3,300 patients died of breast cancer in the Netherlands, making it, together with lung cancer, the most important cause of cancer death among women[1]. However, breast cancer survival has improved for several decades: in the 1970s 5-year relative survival was less than 50%, while for patients diagnosed in 2000-2002 this was 80%[6]. Factors related to the increased survival are, among other things, early detection through breast cancer awareness and screening, resulting in a more favourable stage distribution, and improved (adjuvant) treatment[7].

With the incidence rates of breast cancer increasing and survival rates improving, the number of prevalent breast cancer patients will continue to rise. In 2005 it was estimated that 119,000 patients in the Netherlands were ever diagnosed with breast cancer[6]. Breast cancer prevalence rises with approximately 5% annually[8], and in 2015 the number of (ex-)breast cancer patients might increase to about 194,000[9]. This number is expected to continue to rise also due to demographic developments (age distribution skewed toward old age). A large proportion of these women will still require some form of health care, either for diagnosis and treatment, surveillance during follow-up, or because of recurrences, metastases or new primary malignancies. Breast cancer survivors are at high risk of developing subsequent primary cancers either in the breast or in another organ[10-12].

Chapter 1

Developments in systemic breast cancer treatment

Recent decades have brought a dramatic increase in the number of new agents being investigated and approved for the treatment of patients with breast cancer. The majority of these agents represent a new category of targeted compounds: drugs that interfere with specific targeted molecules needed for carcinogenesis and tumour growth[13]. The treatment of patients with breast cancer with targeted drugs has a long record starting with the approval of tamoxifen for the treatment of hormone (oestrogen) receptor positive metastatic breast cancer in the seventies of the last century[14]. Since then, the list of oncology drug targets in breast cancer patients has expanded including aromatase (aromatase inhibitors), epidermal growth factor receptor 2 (trastuzumab) and vascular endothelial growth factor (bevacizumab)[15]. These targeted drugs together with the conventional chemotherapeutics that interfere with rapidly dividing cells, result in many systemic treatment options to choose from when treating the breast cancer patient.

New morbidities after breast cancer diagnosis and treatment

Current systemic breast cancer treatment is often dispensed next to surgery and radiotherapy and mainly consists of chemotherapeutics administered concurrently or in specified sequential regimens followed by hormonal therapy in patients with hormone positive breast cancer. These approaches can increase the efficacy of breast cancer treatment, but, at the same time, may generate new morbidities that need to be recognized.

Each type of breast cancer treatment may create various morbidities. Radiation therapy may have both localized side effects (such as skin irritation after external radiation) and more general side effects (such as fatigue). Morbidities after radiotherapy are often temporary, but late effects, such as cardiovascular disease, may occur[16, 17]. Morbidities after surgical treatment are decreased due to the less invasive diagnostic and treatment techniques, such as sentinel lymph node biopsy and lumpectomy. However, lymphoedema remains a clinically relevant complication[18]. Ovarian ablation in premenopausal women with hormone receptor-positive breast cancer by e.g. luteinizing hormone releasing hormone (LHRH) agonists, causes menopause-related symptoms such as increased risk of bone loss and cardiovascular events[19]. Endocrine treatment with tamoxifen can cause, next to menopause-related symptoms, much more serious rare morbidities such as endometrial cancer, cataract and thromboembolism[20]. The most common late effect associated with aromatase inhibitors is bone loss[21]. Long-term risks after chemotherapy depend on the specific treatment received. Next to menopause-related symptoms in pre-menopausal women due to amenorrhea, cardiotoxicity is a complication that is rare after chemotherapeutic treatment with some agents, but may occur in >20% of patients treated with doxorubicin, daunorubicin or fluorouracil[22, 23]. Moreover, the risk of cardiotoxicity with

the targeted drug trastuzumab has been reported to be 4% with monotherapy and 27% when administered in combination with anthracyclines[24]. Other chemotherapy related long-term treatment complications are acute leukaemia and myelodysplasia depending on the type of cytotoxic drugs received[25] and impaired cognitive functioning depending on chemotherapy dose and duration[26].
So, new morbidities resulting from breast cancer treatment may be acute, late, reversible, or persistent. Acute, short-term side effects occur during treatment and many are reversible and treatable. Long-term morbidities occur during treatment and may or may not be permanent. Late effects may emerge weeks or months after treatment is completed or even sometimes not be evident until many years later. Serious late and long-term irreversible morbidities are of most concern especially as they are potentially life shortening.

Need for a new data source for pharmacoepidemiological studies in breast cancer patients

Efforts to treat breast cancer are all aimed at maximizing the changes for a healthy life while, at the same time, minimizing new morbidities. Documenting how breast cancer is treated and how these treatments affect the patient, becomes crucial for determining whether these interventions are tolerable and acceptable and provide significant clinical benefits. While effectiveness and safety of breast cancer therapies are thoroughly studied in randomized clinical trials, few data are available on these parameters in a daily practice setting. Daily clinical practice differs from the experimental setting with respect to the heterogeneity of patients, their age, treatments and co-medication. Moreover, important side effects may not be detectable in clinical trials since the frequency of many adverse events is low and adverse effects of cancer therapies may occur many years after drug administration.[27-29]
With the increasing number of patients who were ever diagnosed with breast cancer and the increase in the number of new agents being approved for the treatment of patients with breast cancer, there is a need for a new data source that facilitates post-approval drug utilization, (cost-)effectiveness and safety studies on anti-cancer drugs among breast cancer patients. Linkage of cancer registry data to an administrative healthcare database that includes information on drug use and (co-)morbidities makes this type of research in breast cancer patients possible.

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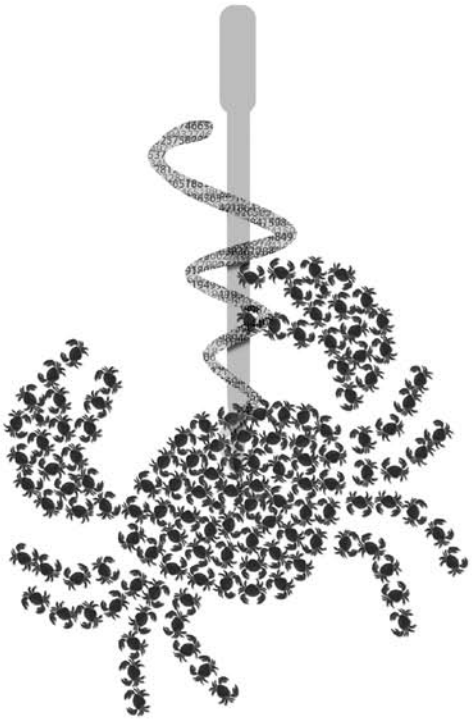
1.2 Outline



Outline

The main objectives of the studies described in this thesis were:

1. To explore whether the linkage of the Eindhoven Cancer Registry and PHARMO Record Linkage System would create a good data source for pharmacoepidemiological studies in cancer patients.
2. To assess systemic breast cancer treatment in daily clinical practice, including chemotherapy and endocrine therapy.
3. To define incidence of morbidities after breast cancer diagnosis and treatment.

Part I

To create a unique source for numerous types of pharmacoepidemiological studies in cancer patients we investigated whether the linkage of the Eindhoven Cancer Registry (ECR) and the PHARMO Record Linkage System (PHARMO RLS) was feasible and valid **(Chapter 2.3)**. This linkage included all cancer sites; however, as the size of the created ECR-PHARMO cohort was too small to study rare cancers, the study population for this thesis included the largest study cohort: breast cancer patients.

Part II

Trends in the use of adjuvant systemic treatment (chemotherapy and/or hormonal therapy) in daily clinical practice were determined using solely data from the ECR **(Chapter 3)**. Expanding data from the included breast cancer cohort with data from the PHARMO RLS allowed us to investigate the type of chemotherapy regimens used with detailed information on the administered intravenous chemotherapies obtained from the PHARMO in-hospital pharmacy database **(Chapter 4)**. Data from the PHARMO community pharmacy database was used to determine the treatment pattern of endocrine therapy use of breast cancer patients living in the ECR-PHARMO catchment area **(Chapter 5)**.

Part III

In this part of the thesis we determined the incidence of morbidities after breast cancer diagnosis and treatment. First, we assessed the incidence of cardiovascular events among breast cancer patients after chemotherapy **(Chapter 6)**. Second, the incidence of myocardial infarction, ischaemic stroke and pulmonary embolism after hospitalisation for breast cancer was determined **(Chapter 7)**. For the latter, solely data from the

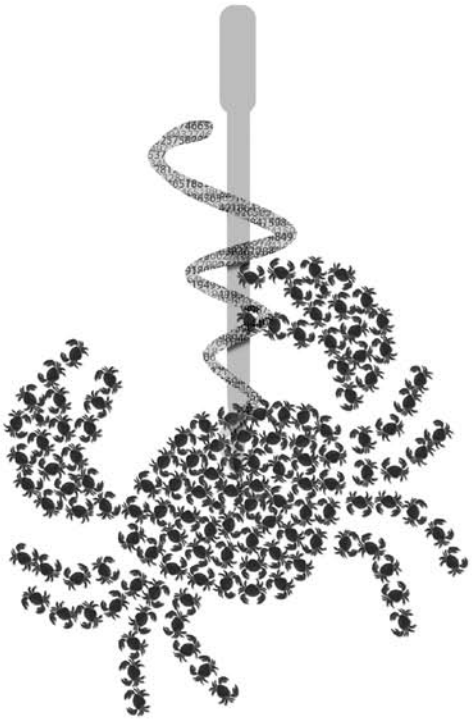
PHARMO RLS were used as this resulted in a larger cohort of breast cancer patients (with less detailed information on the disease) which was desirable to be able to study these rare events.

PART IV

Finally, this thesis ends with an overview of linked databases comparable to the linked ECR-PHARMO cohort **(Chapter 8.2)**. In the general discussion the main results of the studies on breast cancer treatment and related morbidities are considered. We conclude with future perspectives for research with the linked ECR-PHARMO cohort and possible expansion of this cohort.

CHAPTER 2 METHODS

2.1 Data sources



Eindhoven Cancer Registry

The Eindhoven Cancer Registry (ECR) is a population-based registry, maintained by the Comprehensive Cancer Centre South, which was started in 1955 as part of a programme for nation-wide cancer registration in the area of southeastern North Brabant[1]. Data on all new cancer patients are collected directly from pathology reports and patients' medical records. The registry was started in three hospitals in Eindhoven and gradually expanded to include the south eastern part of the province of North Brabant, the northern part of the province of Limburg (since 1970) and the middle and southwestern part of North Brabant since 1986 (except the small most western part) (Figure 1). Other regional registries had discontinued their activities, until a successful nationwide program was re-established since 1984. Since 1989 the whole Dutch population is covered by regional cancer registries, which established the National Cancer Registry.

Figure 1. The current area of the Eindhoven Cancer Registry of the Comprehensive Cancer Centre South

The area in the population-based ECR is now served by 10 general hospitals at 16 locations and two large radiotherapy institutes and covers a demographic region with 2.4 million inhabitants. The region is characterized by good access to medical care without financial obstacles. The distance to a hospital has always been less than 30 kilometres. The area does not contain university or specialized cancer hospitals. There are six pathology laboratories, all participating in the nationwide PALGA network[2, 3], which also notifies the regional cancer registries. The cancer registry receives lists of newly diagnosed patients on a regular base from the pathology departments. In addition, the medical records departments of the hospitals provide lists of outpatients and hospitalized cancer patients. Following this notification, the medical records of newly diagnosed patients (and tumours) are collected, and trained registrars from the cancer registry abstract the required information. Data are

checked for duplicate records. Patients who live in the catchment area of the ECR, but are diagnosed in hospitals elsewhere in the Netherlands, are regularly retrieved from all other Dutch cancer registries since 1989. Before this year it was done directly through retrievals at all the cancer centres.

Staging

Staging of breast cancer is categorised according to the TNM-classification developed and maintained by the International Union Against Cancer (UICC)4. The TNM classification is based on: 1) the size of the tumour (T), 2) whether or not the tumour has spread to the lymph nodes in the armpits (N), and 3) whether the tumour has metastasized (M).

Histological classification

Breast tumours were classified based on site (topography) and morphology (histology), according to the WHO International Classification of Diseases for Oncology (ICD-O)[5]. Histologic tumour grade was recorded as: well differentiated (low grade), moderately differentiated (intermediate grade), or poorly differentiated (high grade).

Receptor status

Breast cancer cells may or may not have three important receptors: Oestrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal growth factor Receptor 2 (Her2/neu; also known as ErbB-2). Since 1984, ER and PR status have been recorded by the ECR on each woman diagnosed with breast carcinoma which was determined by means of immunohistochemistry. The result of hormone receptor status was recorded as 'positive', 'weakly positive' and 'negative'. In this thesis, tumours coded as 'weakly positive' in the pathology reports were also classified in the 'positive' group. For hormone receptor status one combined variable was created with the following subgroups: ER+ and/or PR+; ER- and PR-; unknown.

Since 2005, Her2/neu status was recorded in the ECR on a routine basis. Her2-positivity was recorded using a widely recommended testing algorithm[6, 7]. An immunohistochemistry (IHC) score 3+ was considered positive. When IHC was inconclusive (2+), an additional fluorescent in situ hybridization (FISH) test was indicated. IHC score 3+ or a positive FISH test was considered indicative for Her2/neu overexpression.

Initial treatment

Initial treatment (i.e. treatment given or planned within the first six months after diagnosis) was recorded in the ECR, including radiotherapy (yes/no), chemotherapy (yes/no), endocrine treatment (yes/no) and surgery. Details on the type of surgical procedure were recorded as well, such as breast conserving surgery or mastectomy with or without axillary dissection. Moreover, the sequence of breast-cancer treatment was registered to define whether breast-cancer treatment had been tumour-removing surgery followed by chemotherapy and/or radiation therapy, or whether chemotherapy was started before surgery (neoadjuvant chemotherapy).

Co-morbidity

Since 1993, the registry also records co-morbidity according to a slightly adaptation of the list of serious diseases drawn up by Charlson and colleagues.[8]

Table 1. Classification of co-morbidity, modified version of the list of Charlson *et al.*[8]

Co-morbidities
Chronic obstructive pulmonary disease (COPD)
Cardiovascular disease: myocardial infarction, cardiac insufficiency, angina pectoris, coronary artery bypass graft (CABG)
Peripheral arterial disease: intermittent claudication, abdominal aneurysm, surgical intervention
Cerebrovascular diseases (cerebrovascular accident, hemiplegia)
Other malignancies (except basal cell carcinoma)
Hypertension
Diabetes mellitus
Other:
Autoimmune diseases: sarcoidosis, Wegener's disease, systemic lupus erythematosis (SLE)
Rheumatoid arthritis
Kidney diseases: glomerulonephritis, pyelonethritis
Gastrointestinal: stomach ulcer and resection, colitis
Liver diseases: cirrhosis, hepatitis
Dementia
Chronic infections

In short, the following important conditions were recorded (Table 1): chronic obstructive pulmonary diseases (COPD), cardiovascular and cerebrovascular diseases, other malignancies (excluding basal cell carcinoma of the skin), and diabetes mellitus. Furthermore, hypertension, connective tissue diseases, rheumatoid arthritis, kidney, bowel, and liver diseases, dementia, tuberculosis, and other chronic infections were also recorded.[9, 10]

Socio-economic status

An indicator of socio-economic status developed by Statistics Netherlands was used.[11] At the six-position level of postal code, data on household income and the economical value of the house are available from fiscal data from the year 2000. Within each postal code there are about 17 households, so this aggregate measure counts for a very small geographic area, which enhances the reliability. Furthermore, the use of routinely collected income tax data (no questionnaires or interviews) gives reliable estimates of household income. Socio-economic status was categorized according to quintiles ranging from 1 (low) to 5 (high), with a separate class for postal codes with a care providing institution (such as a

nursing home). This measure is assumed to be valid ten years before and after the set year (2000). Socio-economic differences based on neighbourhood data have proven to be a fairly good reflection of socio-economic differences at an individual level.[12]

PHARMO Record Linkage System

The PHARMO Record Linkage System (PHARMO RLS)[13] is a population-based patient-centric data tracking system which started in 1986 including high quality and complete information of approximately 3 million inhabitants of 65 municipal areas in the Netherlands. The central patient database is linked to more than ten databases using different record linkage algorithms.[14-17] Databases relevant for observational cancer research include virtual complete longitudinal data obtained from hospital discharge records (Dutch National Medical Registration: LMR), community pharmacies (out-patient), and a growing number of in-hospital pharmacies (in-patient), clinical laboratories and general practitioners (these last three databases are available for a sub-cohort of the patients included in the PHARMO RLS). The out- and in-patient pharmacy, clinical laboratory and general practitioner database are managed by PHARMO and directly accessible, while permission is needed to use the data from the Dutch National Medical Registration. Moreover, external databases are linked on a patient level to the PHARMO central patient database and can be used on a project basis (after permission from the database holders), such as the Dutch National Pathology Registry (PALGA)[2,3] and the Perinatal Register[18]. Patient-centric information from the databases can be enriched via direct access to the patient or caregivers. A schematic overview of the PHARMO RLS and the created research database is presented in Figure 3. The PHARMO RLS includes a dynamic cohort of patients. Turnover occurs when patients move in and out of the PHARMO RLS catchment area. The records of 'transferred out' patients remain in the database and are available for retrospective studies with the appropriate time periods. Patients can be followed over a long period of time, until: the patient moves out of the PHARMO RLS catchment area; death; end of data collection of one of the databases used in a specific research study; or end of study period of a specific research study.

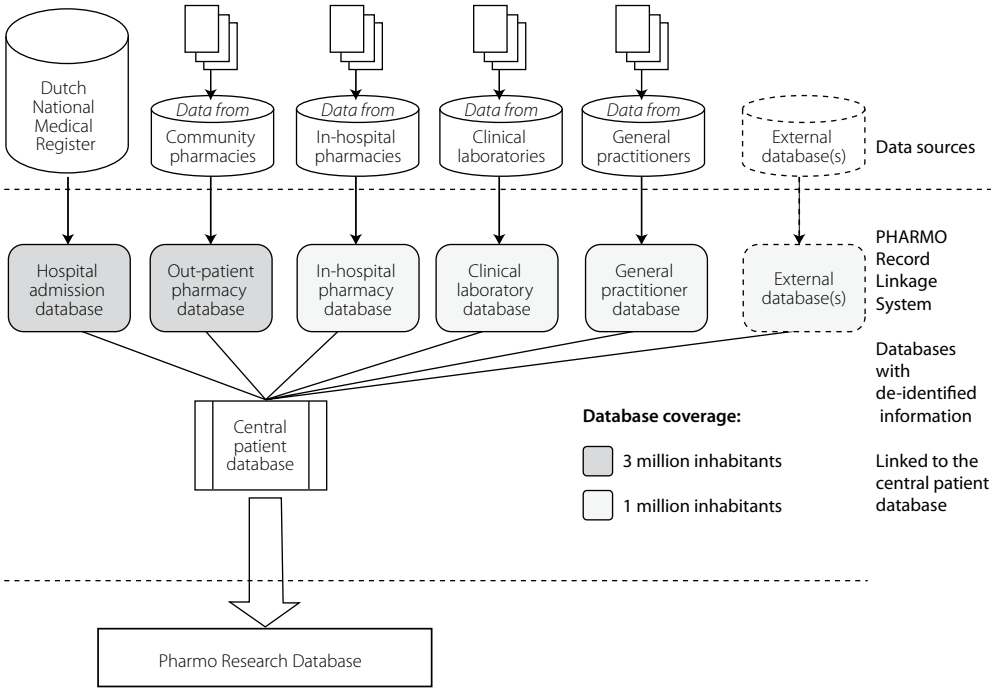


Figure 2. Schematic overview of the PHARMO RLS

Hospital discharge records: Dutch National Medical Register (LMR)

The Dutch National Medical Register (LMR)[19] is a national database of the Netherlands (more than 16 million inhabitants) and linked to the community pharmacy database, this database covers an area of approximately 3 million inhabitants. It comprises all hospital admissions, i.e., admissions for more than 24 hours and admissions for less than 24 hours for which a bed is required. These records include detailed information concerning the primary (mandatory) and secondary (optional) discharge diagnoses, procedures and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases, 9th edition (ICD-9-CM) [20].

Drug dispensing data: via community pharmacies (out-patient)

The community pharmacy database is a nationally representative database which was started in 1986 and includes dispensing information from community pharmacies in the Netherlands. The database includes all general practitioner or specialist prescribed and pharmacy dispensed healthcare products on the Dutch market. The database covers an area of approximately 3 million inhabitants and a total of approximately 4 million patient lives are included in the database. Of each dispensed drug, the Anatomical Therapeutic Chemical (ATC) code[21], dispensing date, prescriber, prescribed dosage regimen, dispensed quantity are available. The duration of use of each dispensing is defined by dividing the number of units dispensed by

the number of units to be used per day, as defined in the pharmacies. The costs of drugs are estimated from a third payer perspective and represent reimbursement costs per dispensing record including VAT. All drug dispensing data in the pharmacy database are encoded according to standards based upon the Z-Index drug database[22]. It is possible to identify and classify drug use followed over time, both on the basis of national and international classification schemes and on the basis of a drug's individual active ingredients and administration forms.

Drug dispensing data: via in-hospital pharmacies (in-patient)

The in-hospital pharmacy database comprises hospital pharmacy data collected in a growing number of general hospitals in the Netherlands (currently a subset of 15 hospitals). The database covers an area of approximately 1 million inhabitants and a total of approximately 2 million patient lives are included in the database. This database includes data on in-patients' medication orders (type of drug, dose, time of administration and duration of use). Chemotherapy data in the in-hospital pharmacy database is not complete for all the included hospital pharmacies, as not all hospitals have data on administered chemotherapies electronically available. For complete registration of the supplied chemotherapies in this database, currently additional non-electronic data from the hospital pharmacies is collected and added to this in-hospital database.

Clinical laboratory data

The clinical laboratory database includes tests taken (e.g., blood tests) and results for all of these tests derived through a total of 9 clinical laboratories in the Netherlands. The database covers an area of approximately 1 million inhabitants and a total of almost 2 million patient lives are included in the database. The clinical laboratories are completely computerized and use auto-analysers for testing, thereby including all test results in a central database. Test results are checked against threshold values and controlled by clinical chemists and those requesting the data, before storing into the database. Errors are corrected and re-analyses can be run on the same (blood tissue or other) sample. Erroneous test results are overwritten by new re-analyses. The laboratory data are of superior quality as everything is recorded independently of the test result or physician. The tests are requested by general practitioners and/or specialists. Laboratory function tests (e.g. lung tests) are structurally collected by only one of the nine laboratories in this database and include mostly only general practitioner requested functional laboratory tests.

General practitioner data

The general practitioner database is a longitudinal observational database that contains data from computer-based patient records of general practitioners (GPs) throughout the Netherlands. GPs receive completely control usage of their data, through the Steering Committee and are permitted to withdraw data for specific research studies. Collaborating practices are located throughout the Netherlands and the collaborating GPs are comparable to other GPs in the country based on age and gender. The general

practitioner database covers an area of almost 1 million inhabitants including almost 2 million patient lives. Detailed clinical information and prescription drugs data are captured in this database, including among other things, demographic data (age, sex, patient identification, GP registration information), diagnoses, physician-linked indications for therapy, co-morbidity, drug prescriptions, laboratory values (e.g. potassium, creatinine), doctor in attendance, referrals to specialists, and a 'medical chart' containing free-text as noted by the general practitioner. Diagnoses and symptoms are recorded based on the International Classification of Primary Care (ICPC) – which can be mapped to ICD-9-CM codes, but diagnoses and complaints can also be entered as free text.[23] Prescription data such as product name, quantity dispensed, dosage regimens, strength and indication are entered into the computer. Prescriptions include medications prescribed by the GP (please note that specialist prescriptions are generally not included in the GP data).

Other databases

Databases that can be linked to the ECR and/or the PHARMO RLS to obtain information relevant for (pharmaco)epidemiologic studies in the area of oncology are the data from the Central Bureau of Genealogy and the Dutch National Pathology Registry.

Survival

Either the ECR or the PHARMO RLS can be linked to data from the Central Bureau of Genealogy (CBG)[24], or the Dutch municipal personal administrative database (GBA)[25] to obtain information on the vital status. The CBG is the Dutch information and documentation centre for genealogy, family history and related sciences. Data are national and collected since October 1994 and include virtually complete coverage of all deceased Dutch citizens. In the GBA all deceased and emigrated persons in the Netherlands are registered.

Pathology

The Dutch nationwide network and registry for histo- and cytopathology (Pathologisch Anatomisch Landelijk Geautomatiseerd Archief; PALGA) contains data of all histological, cytological and autopsy examinations in the Netherlands.[2, 3] PALGA has developed a system of online central archiving for use in direct patient care and research. The data is generated and used voluntarily on daily basis by all (65) departments in the Netherlands. This registration started in 1975 and reached 100% participation in the country since 1990. It also serves for several national population-based screening examinations and forms the main database source for the Dutch regional cancer registries, as described above. PALGA contains abstracts of the pathology reports; an abstract consists of encrypted patient identification; a summary of the report; diagnostic terms being in scope with SNOMED classification. Currently, about 42 million abstracts of more than 10 million patients have been stored and each year more than 2 million abstracts are being added

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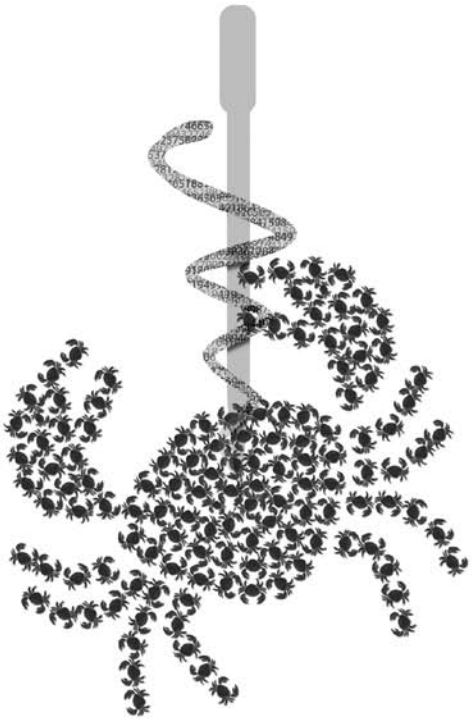
2.2 Concepts of linkage of the ECR and PHARMO RLS



Overlap of ECR and PHARMO RLS

The overlap area of the ECR and the PHARMO RLS in 2008 is presented by the black area in Figure 1. This ECR-PHARMO catchment area includes approximately 1 million inhabitants. Cancer patients living in this catchment area were eligible for linkage and patients who were not a member of the catchment population of both registries were eliminated.

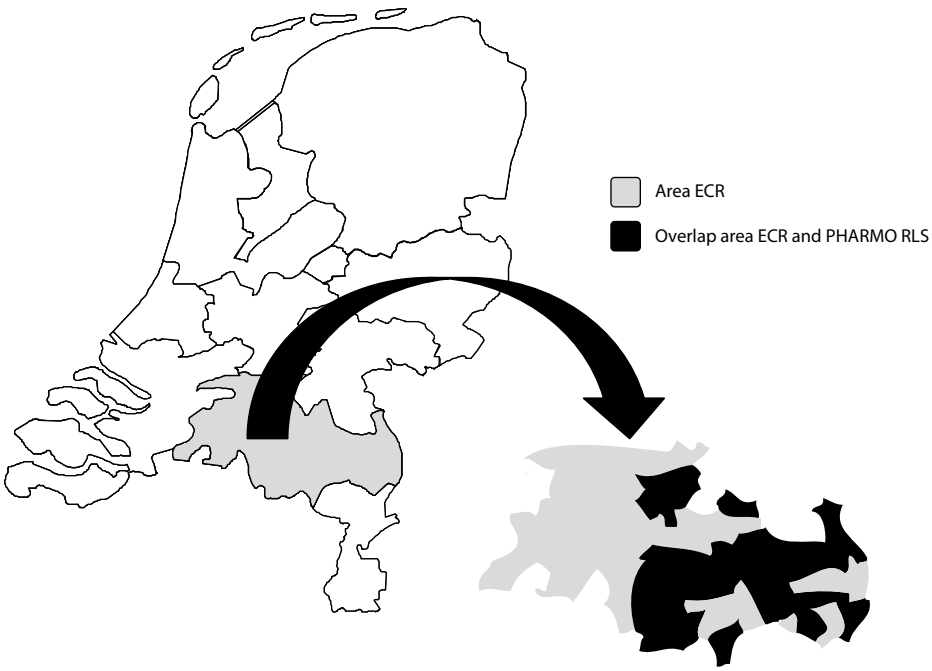


Figure 1. The current area of the Eindhoven Cancer Registry (ECR) and overlap with the area of the PHARMO record linkage system (PHARMO RLS)

Record linkage concepts

Cancer patients registered in the ECR are identified by a unique patient identification number. This number differs from the patient number used in the PHARMO RLS. Moreover, as both databases only contain deidentified information (i.e., all personal identifiers have been removed from the file), no unique personal identifiers are available. As a result, simple deterministic linkage using a patient identifier as linkage key cannot be performed and semi-deterministic or probabilistic linkage is needed. Semi-deterministic and probabilistic linkage are based on the calculation that two records belong to the same patient given a set of on itself not unique patient characteristics. Semi-deterministic linkage has a very high specificity: the number of true matches among the linked pairs is high, provided information of variables is sufficiently high and error rates are not extreme; while it has

a relatively low sensitivity as many true matches may not be found even if error rates per variable are low[1]. As semi-deterministic linkage will not allow any transcription flaws or records with missing data, probabilistic linkage is preferred in our situation. The probabilistic concept assumes that errors and missings will always be present in the record linkage process.

Detailed information on the methodology and the validation of the used record linkage method in this thesis can be found elsewhere[1-8] as well as the used terminology (see Table 1 of Blakely and Salmond[7]). In short, probabilistic linkage includes three major procedures: 1) blocking, 2) matching and 3) linking. Blocking is the process of creating pairs of patient records based on variables that are assumed to be filled-out correctly and do not change over time, such as gender and date of birth. This is the only step in the linkage process that does not allow variables to include transcription flaws. Blocking results in improving matching efficiency (speeding up the matching process) as not all records of the ECR have to be matched to each record of the PHARMO RLS, but only those that are included in a record pair. Following the blocking step, matching occurs, which is the process of comparing pairs of records to predict whether they should be linked. There are several models for statistical probabilistic record linkage and in this thesis Bayesian algorithms[2] are used which are also used for the linkage of the PHARMO hospital discharge records (LMR) to the PHARMO community pharmacy database[3-6]. Multiple variables, such as first initial and zip code are used and the contribution of each matching variable is expressed in a likelihood ratio. By multiplication of these likelihood ratios and prior linkage odds, the odds can be calculated that two records belong to the same patient against that they belong to different patients. Finally, linkage is performed based on the summarized match odds of all variables and a threshold value above which comparison pairs are categorized as links and below which the comparison pairs are categorized as non-links. The optimal single threshold value is the odds at which misclassification is minimal and the pair with the highest weight value above threshold is defined as positive link (same patient) and all other pairs of that specific block are defined as negative links (different patients), as only one file record can logically belong to the same patient. A special situation occurs when more than two records yield the same, highest match odds, which exceeds the threshold. In this situation no decision can be reached as probably both records actually belong to the same patient. These record pairs are defined as unsolvable pairs and need to be solved manually.

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2.3 New opportunities for drug outcomes research in cancer patients: the linkage of the Eindhoven Cancer Registry and the PHARMO Record Linkage System

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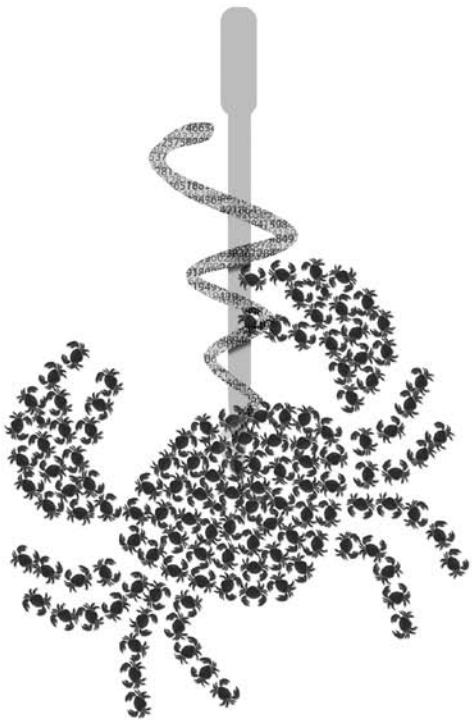
European Journal of Cancer 2010;46:395-404



Abstract

Background:
Insight into co-morbidity and treatment effects is pivotal to improve quality of care for cancer patients.

Objectives:
To determine whether the linkage of the Eindhoven Cancer Registry (ECR) and the PHARMO Record Linkage System (RLS) was technically feasible and to assess which patient-centric data would result from this.

Methods:
The ECR records data on tumour stage and primary treatment of all newly diagnosed cancer patients in the southeastern Netherlands including co-morbidity at diagnosis, whereas the PHARMO RLS includes data from multiple linked observational databases such as data on drug utilization (for both in- and out-patients, including chemotherapy), hospitalisations and clinical laboratory measurements. All patients who lived or had been living in the overlapping area served by the ECR and the PHARMO RLS during 1998-2006 were selected for linkage which was performed with probabilistic medical record linkage.

Results:
The linkage resulted in an ECR-PHARMO cohort of 40,004 cancer patients with a total of 42,767 primary tumours. The cancer patients in the linked ECR-PHARMO cohort were representative for the cancer patients included in the total ECR during 1998-2006. Cancer patients included in the cohorts had a mean history of five years and a mean follow-up ranging from two to more than four years (dependent on the survival rate of the specific cancer type).

Conclusions:
Linkage of ECR and the PHARMO RLS creates the possibility to study patient-centric drug utilization, health resources utilization and their costs, in addition to the effectiveness and safety of pharmaceuticals in routine daily practice in cancer patients.

Introduction

In Europe there are over two million incident patients with cancer every year and it is expected that this number will continue to rise[1]. With the ageing of the population and the increasing survival of cancer patients with co-morbid conditions, cancer is and will become an increasingly important factor in the global burden of disease in the decades to come.

A growing number of cancer patients are treated with novel treatment combinations and targeted therapies are being introduced at relatively early stages of disease progression. While effectiveness and safety of these new therapies are thoroughly studied in randomized clinical trials, little data are available on these parameters in a daily practice setting. Effectiveness of anti-cancer drugs may be different than expected as daily clinical practice differs from the experimental setting with respect to the heterogeneity of patients, their treatments and co-medication. Moreover, important safety issues may not be detectable in clinical trials since the frequency of many adverse events is low and adverse effects of cancer therapies may occur many years after drug administration.[2-4] Balancing effectiveness and adverse effects is therefore a major challenge in the treatment of cancer patients and monitoring post approval drug use is especially important for anti-cancer drugs that receive accelerated FDA and EMEA approval.

Besides monitoring the effectiveness and safety of cancer treatments, pharmaceuticals used for a wide variety of other conditions may be associated with increasing or decreasing risk of cancer, such as non-steroidal anti-inflammatory drugs or lipid lowering drugs[5, 6]. Data to confirm, refute or elaborate on these hypotheses are sparse.

To shed light on the burden of cancer, disease management, safety aspects, co-morbidity patterns and outcomes assessments, follow-up of patients before and after cancer diagnosis in routine daily practice is pivotal. For this, large administrative databases or cancer registries are often used[7]. However, both type of data collections mostly lack detail; either with respect to the incidence and staging of cancer or with respect to (pharmaco)treatments, morbidity and co-morbidity during follow-up[8].

We therefore explored whether the linkage of a regional cancer disease register (Eindhoven Cancer Registration: ECR) and a patient-centric data network including multiple linked observational databases (PHARMO Record Linkage System: PHARMO RLS[9]) was feasible, valid and detailed enough to fulfil the abovementioned information needed. In this manuscript we describe the results of this linkage as well as the patient-centric data on drug treatment (out-patient and in-patient), hospitalisations and clinical laboratory measurements that become available during follow-up before and after cancer diagnosis for the cancer patients present in these linked databases.

Methods

Data sources

The Eindhoven Cancer Registry (ECR) is a population-based registry (covering a demographic region with 2.4 million inhabitants) which is maintained by the Comprehensive Cancer Centre South and collates records on all newly diagnosed cancer patients in the southeastern part of the Netherlands[10, 11]. The ECR is notified for new patients with cancer by six pathology departments, ten general hospitals and two radiotherapy institutes. Trained registry personnel subsequently actively collect on site data on patient characteristics, diagnosis, tumour staging, co-morbidity at diagnosis and treatment received directly after diagnosis (e.g. chemotherapy (yes/no), radiation therapy and surgery).

The PHARMO RLS is a large, patient-centric data network including multiple linked observational databases designed for safety and outcomes research of drugs which collates patient records in 48 geographic defined areas in the Netherlands (covering a demographic region of 3 million inhabitants). The central patient database is linked to more than ten databases using different medical record linkage algorithms.[12-15] Databases relevant for observational cancer research include virtual complete longitudinal data obtained from community pharmacies (out-patient), hospital discharge records (Dutch National Medical Registration: LMR), a mortality registration and a growing number of clinical laboratories, in-hospital pharmacies (in-patient) and general practitioners (these last three databases are available for a sub-cohort of the patients included in the PHARMO RLS).

Both the ECR and the PHARMO RLS are recognized as high quality sources for epidemiological research that collect information in overlapping regions in the Netherlands for a period of at least 10 years.

Medical record linkage

The first step in combining the ECR and the PHARMO RLS was to identify in both databases all patients who lived or had been living in overlapping zip code areas and were diagnosed with cancer in the period 1998-2006. This overlapping catchment area covered all inhabitants of 510 zip codes (approximately 1 million inhabitants).

Because these databases only contain deidentified information (i.e., all personal identifiers have been removed from the file), no unique personal identifiers were available and hence, the linkage of the ECR and the PHARMO RLS had to be based on probabilistic record linkage technology.[16-18] This technology is also used for the linkage of several databases in the PHARMO RLS and involves three major steps: 1) blocking, 2) matching and 3) linking.

1) In the blocking step[17], for each patient in the ECR, data on patients from the PHARMO RLS with similar gender and date of birth were grouped into record pairs. An example of the approach would be as follows: If there were 2 patients with similar gender and date

of birth in the ECR and there were 3 patients in the PHARMO RLS, then the blocking step would result in 6 (2x3) record pairs.

2) In the matching step[17], for each record pair the probability (match odds) that both records of the ECR and the PHARMO RLS belong to the same patient was calculated using Bayesian algorithms[19]. Multiple matching variables available in both databases were used: first initial, first letter last name, soundex code of last name[20], first four characters of the patients' most recent zip code as well as singular variables. The latter represent logical relation between two records, i.e. an extra weight was assigned if a cancer patient from the ECR had been hospitalized for cancer as notified in the hospital discharge records from the PHARMO RLS.

3) Finally, linkage was performed based on the summarized match odds of all variables, the weight value, by applying a threshold weight value[16, 17]. The record pair with the highest cumulative weight value above threshold was defined as positive link (same patient) and all other pairs were defined as negative links (different patients), as only one record could logically belong to the same patient.

Validation

The quality of the medical record linkage process was evaluated in a random sample in which additional person information was obtained from the original patient-centric data sources of the PHARMO RLS (in this case, community pharmacies participating in the PHARMO system) and the ECR, including full name and address of the patients: the "gold standard". Record pairs where manually compared after being blinded with respect to outcome of the above described linkage process. This validation was approved by the privacy committee of the PHARMO Institute for Drug Outcomes Research and met the criteria of the health research code of conduct.[21]

The validation resulted in true and false record pairs and detailed information on the methodology and the validation of the used record linkage method can be found elsewhere[12, 13, 16-19, 22, 23]. A flowchart of the linkage of the ECR to the PHARMO RLS is presented in Figure 1.

Representativeness

The linkage process resulted in a linked ECR-PHARMO cohort. Representativeness to the total ECR population was evaluated by comparing the distribution of gender, age at tumour diagnosis, year of diagnosis and the most common cancer sites. With respect to the latter, unlike other current cancer registries, basal cell carcinoma is also registered in the ECR.[24]

Characteristics per tumour cohort were shown for the total ECR and the linked ECR-PHARMO cohort for the four most common types of cancer (not accounting for basal cell carcinoma): breast cancer, colorectal cancer, lung cancer and prostate cancer.

Illustration of information for different cancer cohorts

An illustration of the information gained from linkage of the ECR and PHARMO RLS was presented for patients included in the breast cancer, colorectal cancer, lung cancer and prostate cancer cohorts. For this, information on history (before cancer diagnosis) and follow-up (after cancer diagnosis) was determined for patients included in the total linked ECR-PHARMO cohort and for patients included in a sub-cohort with information from the clinical laboratory database available (approximately 80% of the patients in the total linked cohort). History was defined as the time between the date of entering the PHARMO RLS to the date of cancer diagnosis as registered in the ECR. Follow-up was defined as the time between date of cancer diagnosis until end of data-collection in the PHARMO RLS (*i.e.* the patient moves out of the PHARMO RLS catchment area), death, or end of the study period (December 31st, 2007), whichever occurred first.

Co-morbidities at diagnosis, medication use, hospitalisation and laboratory measurements during the one year before cancer diagnosis were determined for patients with at least one year history and with data from the clinical laboratory database available. Treatments received, medication use, hospitalisations and laboratory measurements during the one year after cancer diagnosis were determined for patients with at least one year follow-up and with data from the clinical laboratory database available. Co-morbidity at cancer diagnosis and initial therapy were extracted from the ECR and information on co-medication, hospitalisations and clinical laboratory measurement were extracted from the PHARMO RLS. For patients who received chemotherapy, data on the type of cytostatics (defined as ATC code L01) was extracted from both in-hospital pharmacies (in-patient, e.g. cytostatics administered intravenously) and community pharmacies (out-patient, e.g. cytostatics administered orally) for a sub-cohort (approximately 45% of the patients) of the PHARMO RLS.

Data were subsequently analysed using SAS programs that are organised within SAS Enterprise Guide version 4.0 (SAS Institute Inc., Cary, NC, USA). Data management was conducted under UNIX using SAS version 9.1.

Results

Of the 104,562 cancer patients registered in the ECR in the period 1998-2006, 57,612 (55%) patients were not eligible for linkage of which 2,339 (2%) were diagnosed in hospitals elsewhere in the Netherlands and 55,273 (53%) were not living in the ECR-PHARMO catchment area (Figure 1).

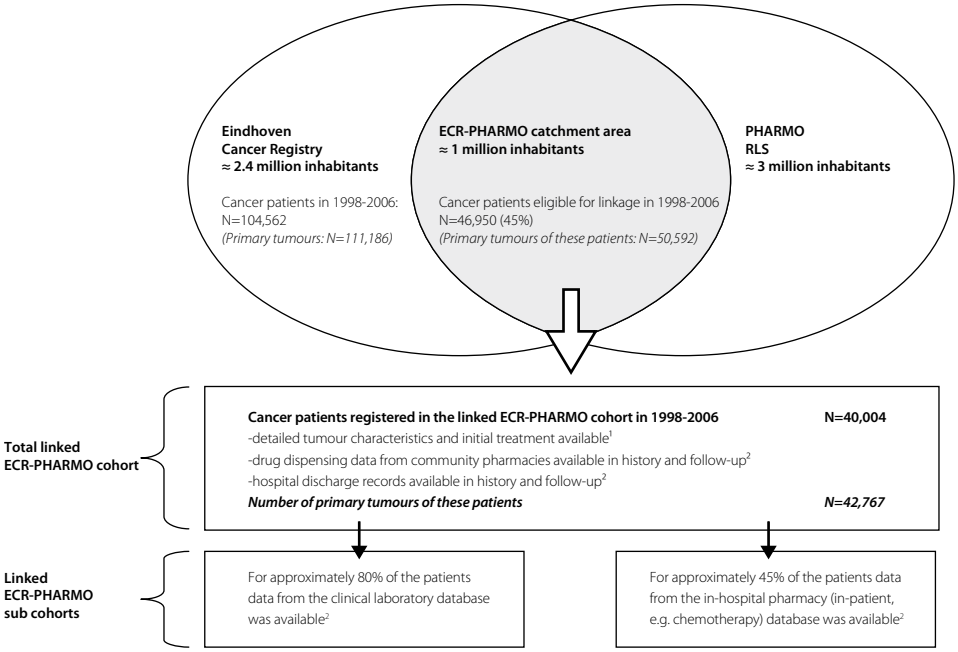


Figure 1. Flowchart of the linkage process and cohort formation

ECR: Eindhoven cancer registry; [1] Data obtained from ECR; [2] Data obtained from PHARMO RLS

Of the remaining 46,950 patients who were eligible for linkage, 40,004 (85%) cancer patients were finally linked and included in the ECR-PHARMO cohort with a total of 42,767 primary tumours.

Table 1. Representativeness of the linked ECR-PHARMO cohort compared to the total ECR in the period 1998-2006 for patients diagnosed with a primary tumour

	Total ECR (N=111,186) n (%)	Linked ECR-PHARMO cohort (N=42,767) n (%)	Difference (% total ECR minus % linked cohort) %
Gender			
Male	57,443 (52)	22,239 (52)	-0.3
Female	53,743 (48)	20,528 (48)	0.3
Age at tumour diagnosis			
≤ 35	3,659 (3)	1,197 (3)	0.5

35 – 49	11,909 (11)	4,277 (10)	0.7
50 – 59	20,322 (18)	7,613 (18)	0.5
60 – 69	29,629 (27)	11,761 (28)	-0.9
70 – 79	30,895 (28)	12,231 (29)	-0.8
89 – 90	13,349 (12)	5,175 (12)	-0.1
≥ 90	1,423 (1)	513 (1)	0.1
Year of diagnosis			
1998-2000	32,784 (30)	11,162 (26)	3.4
2001-2003	37,292 (34)	14,626 (34)	-0.7
2004-2006	41,110 (37)	16,978 (40)	-2.7
Cancer sites			
Skin, Basal Cell Carcinoma	22,693 (20)	9,403 (22)	-1.6
Breast	14,226 (13)	5,545 (13)	-0.2
Colon and Rectum	12,158 (11)	4,804 (11)	-0.3
Lung, Bronchus and Trachea	12,105 (11)	4,395 (10)	0.6
Prostate	9,740 (9)	3,835 (9)	-0.2
Haematolymphopoetic	6,193 (6)	2,285 (5)	0.2
Skin, other	4,185 (4)	1,594 (4)	0.0
Skin, Melanoma	3,469 (3)	1,210 (3)	0.3
Primary Site Unknown	3,129 (3)	1,147 (3)	0.1
Urinary Bladder	2,849 (3)	1,030 (2)	0.2
Stomach	2,545 (2)	935 (2)	0.1
Not further specified	17,894 (16)	6,584 (15)	0.7

ECR: Eindhoven cancer registry

Detailed tumour data and initial treatment data was extracted from the ECR. Drug dispensing data (from community pharmacies) and hospitalisation data was extracted from the PHARMO RLS for all patients included in this linked ECR-PHARMO cohort. Data from the clinical laboratory database was available for approximately 80% of the cancer patients in the linked ECR-PHARMO cohort and data on specific type of cytostatics administered to a patient in-hospital was available for approximately 45% of the cancer patients in the linked ECR-PHARMO cohort.
Validation of a random sample of the linked ECR-PHARMO cohort resulted in 2,887 true positive links, 42 false positive links, 51 false negative links and 9,009 true negative links, yielding a sensitivity of 98.3% (95% confidence interval (CI): 97.7% - 98.7%) and a specificity of 99.5% (95% CI: 99.4% - 99.7%).

Table 2. Representativeness of breast, colorectal, lung and prostate cancer cohorts[1] extracted from the total ECR compared to the cohorts extracted from the linked ECR-PHARMO cohort in the period 1998-2006

	Breast		Colon and Rectum		Lung, Bronchus and Trachea		Prostate	
Character-istics	**Total ECR (N=14,226) n (%)**	**Linked ECR-PHARMO (N=5,545) n (%)**	**Total ECR (N=12,105) n (%)**	**Linked ECR-PHARMO (N=4,804) n (%)**	**Total ECR (N=12,158) n (%)**	**Linked ECR-PHARMO (N=4,395) n (%)**	**Total ECR (N=9,740) n (%)**	**Linked ECR-PHARMO (N=3,835) n (%)**
Gender								
Male	99 (0.7)	34 (0.6)	6,419 (53)	2,584 (54)	8,720 (72)	3,176 (72)	9,740 (100)	3,835 (100)
Female	14,127 (99)	5,511 (99)	5,686 (47)	2,220 (46)	3,438 (28)	1,219 (28)	NA	NA
Age at tumour diagnosis								
≤ 35	418 (3)	139 (3)	75 (0.6)	25 (0.5)	40 (0.3)	13 (0.3)	1 (<0.1)	0 (-)
35 – 49	3,249 (23)	1,178 (21)	650 (5)	252 (5)	816 (7)	252 (6)	75 (0.8)	26 (0.7)
50 – 59	3,523 (25)	1,375 (25)	1,881 (16)	715 (15)	2,253 (19)	781 (18)	1,143 (12)	420 (11)
60 – 69	3,105 (22)	1,272 (23)	3,409 (28)	1,361 (28)	3,969 (33)	1,479 (34)	3,576 (37)	1,413 (37)
70 – 79	2,507 (18)	1,031 (19)	4,036 (33)	1,653 (34)	4,056 (33)	1,489 (34)	3,778 (39)	1,497 (39)
89 – 90	1,265 (9)	488 (9)	1,884 (16)	731 (15)	998 (8)	371 (8)	1,104 (11)	454 (12)
≥ 90	159 (1)	62 (1)	170 (1)	67 (1)	26 (0.2)	10 (0.2)	63 (0.6)	25 (0.7)
Tumour stage								
I	5,710 (40)	2,310 (42)	2,279 (19)	931 (19)	2,062 (17)	768 (18)	240 (3)	108 (3)
II	6,137 (43)	2,366 (43)	3,776 (31)	1,476 (31)	679 (6)	268 (6)	6,185 (64)	2,432 (63)
III	1,426 (10)	556 (10)	2,945 (24)	1,244 (26)	3,775 (31)	1,389 (32)	1,397 (14)	509 (13)
IV	621 (4)	225 (4)	2,356 (20)	912 (19)	4,039 (33)	1,410 (32)	1,589 (16)	663 (17)
Other/unknown	332 (2)	88 (2)	749 (6)	241 (5)	1,603 (13)	560 (13)	329 (3)	123 (3)

ECR: Eindhoven cancer registry; [1] four most common types of cancer not accounting for basal cell carcinoma; NA: not applicable.

The cancer patients included in the linked ECR-PHARMO cohort were representative for the cancer patients included in the total ECR in the period 1998-2006 as shown in Table 1. The difference in percentage between these two cohorts (% total ECR minus % linked ECR-PHARMO cohort) showed that patients who were linked tended to be somewhat older, were diagnosed in the more recent years (2004-2006) and were diagnosed with the more common types of tumours. Gender, age and tumour stage distribution for the patients included in the breast, colorectal, lung and prostate cancer cohorts were similar for the total ECR and the linked ECR-PHARMO cohorts (Table 2).

Table 3. History before and follow-up after cancer diagnosis of patients included in the linked ECR-PHARMO cohorts and sub-cohort in the period 1998-2006

Characteristics	Breast (N=5,545)	Colon and Rectum (N=4,804)	Lung, Bronchus and Trachea (N=4,395)	Prostate (N=3,835)
History (before cancer diagnosis)				
Mean ± SD (years)	4.9 ± 3.5	5.2 ± 3.6	5.1 ± 3.5	5.2 ± 3.5
Median (interquartile range, years)	4.6 (2.1-7.1)	4.9 (2.2-7.4)	4.9 (2.2-7.4)	4.9 (2.4-7.4)
Patients with ≥ 1 year history [1]				
in total linked cohort	4,687 (85%)	4,153 (86%)	3,776 (86%)	3,324 (87%)
and with information from the clinical laboratory database available (sub-cohort) [2]	3,691 (67%)	3,431 (71%)	3,006 (68%)	2,829 (74%)
Follow-up (after cancer diagnosis)				
Mean ± SD (years)	4.4 ± 2.6	3.4 ± 2.6	2.0 ± 2.2	3.9 ± 2.4
Median (interquartile range, years)	4.1 (2.3-6.3)	2.8 (1.3-5.2)	1.1 (0.5-2.6)	3.5 (1.9-5.6)
Patients with ≥ 1 year follow-up [3]				
in total linked cohort	5,164 (93%)	3,910 (81%)	2,403 (55%)	3,541 (92%)
and with information from the clinical laboratory database available (sub-cohort) [2]	4,005 (72%)	3,187 (66%)	1,856 (42%)	2,954 (77%)

[1] history was defined as time between the date of entering the PHARMO RLS to the date of cancer diagnosis; [2] information from the clinical laboratory database was available for approximately 80% of the patients in the total linked cohort; [3] follow-up was defined as the time between date of cancer diagnosis until end of data-collection in the PHARMO RLS (i.e. the patient moves out of the PHARMO RLS catchment area), death, or end of the study period (December 31st, 2007), whichever occurred first.

Patients diagnosed with the four most common types of cancer included in the linked ECR-PHARMO cohort were followed before and after cancer diagnosis to assess patients' baseline covariate status before diagnosis and (adverse) events after diagnosis and treatment. History before cancer diagnosis was approximately five years and similar for all four cancer types, while follow-up after cancer diagnosis was dependent on patients' survival and ranged from a mean follow-up of two years for lung cancer patients to more than four years for breast cancer patients (Table 3).

Of the cancer patients included in the four major linked cancer cohorts who were registered one year or more in the PHARMO RLS before cancer diagnosis and with data from the clinical laboratory database available, co-morbidities at diagnosis and medication, hospitalisation and laboratory measurements in the one year before cancer diagnosis are presented in Table 4. For the most common co-morbidities: cardiovascular disease (including hypertension), diabetes and respiratory disease, the percentage of patients with these co-morbidities at diagnosis as registered in the ECR, and the percentage of patients using medications or who had been hospitalized for these co-morbidities as registered in the PHARMO RLS, were in the same range per type of co-morbidity. Moreover, to give an impression of the type of laboratory measurements available, the percentage of patients with laboratory measurements related to their co-morbidities in the year before cancer diagnosis are presented.

Of the cancer patients included in the four major linked cancer cohorts who were registered one year or more in the PHARMO RLS after cancer diagnosis and with data from the clinical laboratory database available, initial therapies, other received medications, hospitalisations and laboratory measurements are presented in Table 5. Type of cytostatics administered to a patient was available from the PHARMO RLS from in-hospital pharmacy data (in-patient) and the community pharmacy data (out-patient), for 41% (N=465) of the breast cancer patients to 55% (N=363) of the lung cancer patients who received chemotherapy. In Table 5 an overview of the most common types of cytostatics (categories of cytostatics) per cancer type are shown, not taking into account combinations of cytostatics used in the same treatment regimen. Next to data on cancer treatment, the percentage of patients using medications or who had been hospitalized during the first year after cancer diagnosis for the three most common co-morbidities are shown. Moreover, an example is shown of the type of laboratory measurements patients had related to patients' cancer diagnosis and co-morbidities during the one year follow-up.

Table 4. Co-morbidities at diagnosis and medication, hospitalisation and laboratory measurements during the one year *before* diagnosis of patients with breast, colorectal, lung and prostate cancer, extracted from the linked ECR-PHARMO sub-cohort in the period 1998-2006 [1]

Characteristics	Breast (N=3,691) n (%)	Colon and Rectum (N=3,431) n (%)	Lung, Bronchus and Trachea (N=3,006) n (%)	Prostate (N=2,829) n (%)
Co-morbidity at diagnosis; Data obtained from ECR				
Number of co-morbidities at diagnosis				
None	1,781 (48)	1,028 (30)	709 (24)	936 (33)
1	867 (24)	1,012 (30)	949 (32)	870 (31)
≥ 2	635 (17)	1,090 (32)	1,152 (38)	752 (27)
Unknown	408 (11)	301 (9)	196 (7)	271 (10)

Characteristics	Breast (N=3,691) n (%)	Colon and Rectum (N=3,431) n (%)	Lung, Bronchus and Trachea (N=3,006) n (%)	Prostate (N=2,829) n (%)
Type of co-morbidities at diagnosis				
Cardiovascular disease	1,030 (28)	1,513 (44)	1,333 (44)	1,220 (43)
Diabetes	294 (8)	404 (12)	328 (11)	251 (9)
Respiratory disease	202 (5)	351 (10)	794 (26)	289 (10)
Medication and/or hospitalisations during one year of history; Data obtained from PHARMO RLS				
Cardiovascular disease				
Hospitalisations	108 (3)	230 (7)	223 (7)	164 (6)
Medications	1,586 (43)	1,967 (57)	1,663 (55)	1,628 (58)
Hospitalisation and/or medication[2]	1,606 (44)	1,990 (58)	1,691 (56)	1,645 (58)
Diabetes				
Hospitalisations	5 (0.1)	8 (0.2)	6 (0.2)	6 (0.2)
Medications	273 (7)	365 (11)	273 (9)	245 (9)
Hospitalisation and/or medication[2]	274 (7)	367 (11)	276 (9)	248 (9)
Respiratory disease				
Hospitalisations	21 (0.6)	54 (2)	165 (6)	49 (2)
Medications	374 (10)	479 (14)	1,026 (34)	424 (15)
Hospitalisation and/or medication[2]	382 (10)	500 (15)	1,080 (36)	442 (16)
Clinical laboratory measurements during one year of history; Data obtained from PHARMO RLS				
Cardiovascular related measurements e.g.:				
LDL cholesterol	688 (19)	940 (27)	899 (30)	938 (33)
HDL cholesterol	765 (21)	1,024 (30)	972 (32)	1,038 (37)
Diabetes related measurements e.g.:				
HbA1c, blood glucose	421 (11)	560 (16)	451 (15)	440 (16)

ECR: Eindhoven cancer registry; SD: standard deviation; LDL: low density lipoprotein; HDL: high density lipoprotein; HbA1c: glycated haemoglobin; [1] patients with at least 1 year of history, defined as time between the date of entering the PHARMO RLS to the date of cancer diagnosis; [2] numbers do not add up as hospitalized patients mostly also have received medications

Table 5. Received treatments, medications, hospitalisations and laboratory measurements during the one year *after* diagnosis of patients diagnosed with breast, colorectal, lung and prostate cancer extracted from the linked ECR-PHARMO sub-cohort in the period 1998-2006 [1]

Characteristics	Breast (N=4,005) n (%)	Colon and Rectum (N=3,187) n (%)	Lung, Bronchus and Trachea (N=1,856) n (%)	Prostate (N=2,954) n (%)
Initial therapies; Data obtained from ECR				
Received initial therapies				
Surgery	3,828 (96)	2,973 (93)	569 (31)	462 (16)
Radiation therapy	2,767 (69)	822 (26)	757 (41)	1,242 (42)
Hormonal therapy	1,635 (41)	0 (-)	0 (-)	1,383 (47)
Chemotherapy	1,127 (28)	902 (28)	656 (35)	15 (0.5)
Of those who received chemotherapy, type of cytostatics received during one year of follow-up; *Data obtained from PHARMO RLS for a sub-cohort* [2,3]				
	(N=465)	***(N=411)***	***(N=363)***	***(N=7)*** [4]
Pyrimidine analogues	304 (65)	387 (94)	151 (42)	-
Platinum compounds	0 (-)	174 (42)	271 (75)	-
Cyclophosphamide	425 (91)	4 (1)	70 (19)	-
Anthracyclines	359 (77)	0 (-)	67 (18)	-
Etoposide	0 (-)	0 (-)	136 (37)	-
Methotrexate	78 (17)	0 (-)	0 (-)	-
Monoclonal antibodies	31 (7)	33 (8)	0 (-)	-
Taxanes	44 (9)	0 (-)	36 (10)	-
Irinotecan	0 (-)	58 (14)	0 (-)	-
Vinca alkaloids	0 (-)	0 (-)	18 (5)	-
Medication and/or hospitalisations during one year of follow-up; Data obtained from PHARMO RLS				
Cardiovascular disease				
Hospitalisations	132 (3)	185 (6)	136 (7)	198 (7)
Medications	1,821 (45)	1,896 (59)	1,122 (60)	1,824 (62)
Hospitalisation and/or medication [5]	1,842 (46)	1,922 (60)	1,136 (61)	1,843 (62)
Diabetes				
Hospitalisations	6 (0.1)	4 (0.1)	3 (0.2)	1 (<0.1)
Medications	317 (8)	340 (11)	175 (9)	285 (10)
Hospitalisation and/or medication [5]	319 (8)	340 (11)	175 (9)	285 (10)

Characteristics	Breast (N=4,005) n (%)	Colon and Rectum (N=3,187) n (%)	Lung, Bronchus and Trachea (N=1,856) n (%)	Prostate (N=2,954) n (%)
Respiratory disease				
Hospitalisations	42 (1)	52 (2)	197 (11)	58 (2)
Medications	405 (10)	409 (13)	779 (42)	460 (16)
Hospitalisation and/or medication [5]	434 (11)	430 (13)	857 (46)	478 (16)
Clinical laboratory measurements during one year of follow-up; Data obtained from PHARMO RLS				
Tumour markers, e.g.				
PSA	NA	392 (12)	212 (11)	2,528 (86)
CEA	476 (12)	1,862 (58)	92 (5)	82 (3)
CA 15.3	412 (10)	15 (0.5)	10 (0.5)	NA
Blood level/count, e.g.				
Haemoglobin	3,502 (87)	2,986 (94)	1,631 (88)	2,161 (73)
Leukocytes	2,807 (70)	2,804 (88)	1,578 (85)	1,665 (56)
Thrombocytes	2,307 (58)	2,449 (77)	1,451 (78)	1,053 (36)
Liver enzymes, e.g.				
ALT	2,512 (63)	2,538 (80)	1,450 (78)	1,172 (40)
AST	2,102 (52)	2,334 (73)	1,368 (74)	909 (31)
ALP	1,545 (39)	1,798 (56)	1,066 (57)	924 (31)
GGT	1,811 (45)	2,014 (63)	1,074 (58)	734 (25)
LDH	684 (17)	717 (22)	409 (22)	181 (6)

ECR: Eindhoven cancer registry; SD: standard deviation; NA: not applicable; PSA: prostate specific antigen; CEA: carcinoembryonic antigen; CA: carcinogen antigen; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma glutamyl transpeptidase; LDH: lactate dehydrogenase; [1] patients with at least one year of follow-up, defined as the time between date of cancer diagnosis until end of data-collection in the PHARMO RLS (i.e. the patient moves out of the PHARMO RLS catchment area), death, or end of the study period (December 31st, 2007), whichever occurred first; [2] for a sub-cohort of approximately 45% of the patients, both in-hospital pharmacy (e.g. cytostatics administered intravenously) and community pharmacy (e.g. cytostatics administered orally) data available; [3] numbers do not add up as patients may have received multiple cytostatics, pyrimidine analogues included: fluorouracil, gemcitabine and capecitabine; platinum compounds included: oxaliplatin (colorectal cancer) and cisplatin (lung cancer); anthracyclines included: doxorubicin and epirubicin; monoclonal antibodies included: trastuzumab (breast cancer) bevacizumab (colorectal cancer) and cetuximab (colorectal cancer); taxanes included: docetaxel and paclitaxel; [4] not further specified, due to low numbers; [5] numbers do not add up as hospitalized patients mostly also have received medications

Discussion

In this study, the ECR and the PHARMO RLS were linked creating a novel ECR-PHARMO population-based and patient-centric cohort that provides an excellent opportunity to gain real-life insights into drug utilization (for both in- and out-patients), health resources utilization and their costs. Moreover, the effectiveness and safety of pharmaceuticals in cancer patients outside the clinical trial setting can be assessed using hospitalisation data and clinical laboratory measurements. This linkage also enables research to study cancer as an adverse event of a wide range of pharmaceuticals. By widely communicating study results and providing feedback to clinicians on therapeutic choices made and subsequent outcomes, research performed with the ECR-PHARMO cohort can lead to a better understanding of burden of cancer and offer potential for improvements in disease management in the field.

Of the 46,950 patients that were eligible for linkage, 85% could be accurately linked with an overall specificity of 99.5% and a sensitivity of 98.3%. The quality of the linkage is comparable to linkage based on a unique patient identifier. The 15% eligible ECR cancer patients that were not linked can be explained by overestimation of the number of eligible cancer patients as it is extremely difficult to define the exact overlapping catchment area of the ECR and the PHARMO RLS: eligible ECR patients might not turn up in the PHARMO RLS when 1) they migrate out of the catchment area, 2) are institutionalized or 3) fill their prescriptions in pharmacies outside the catchment area of the PHARMO RLS while they are living inside the defined catchment area. Next to eligibility, patients might be lost in the blocking step of the linkage as the blocking variables date of birth and gender are subject to recording errors, which will directly lead to a non-link. This is not the case with the variables used in the probabilistic matching step, however, in this step it is inevitable that there is some degree of uncertainty by which true links might have been missed.

Currently, cancer patients included in the cohorts had a mean history of five years and a mean follow-up ranging from two to more than four years (dependent on the survival rate of the specific cancer type) to study utilization-related outcomes, such as medication, clinical laboratory measurements and (re)hospitalisation for complications following cancer diagnosis and treatment. This follow-up period will increase for the cancer survivors as both the ECR and the PHARMO RLS are prospective data collection systems. The longitudinal and patient-centric nature of these data is a major benefit, because they allow for evaluation of health care utilization both before and after cancer diagnosis, as well as enable evaluation of long-term outcomes often missed in clinical trials.

The ECR and the PHARMO RLS currently collect data of more than 2 and 3 million inhabitants, respectively. However, only 45% of the catchment areas (approximately 1 million inhabitants) overlap. The size of the linked ECR-PHARMO cohort can be doubled in the future by either expanding the PHARMO RLS in the ECR region or by linkage of the PHARMO RLS to other cancer registries in the Netherlands.

At the time of this study, recruitment of all clinical laboratories in the ECR-PHARMO

region was not yet completed, resulting in clinical laboratory findings for around 80% of all patients. Moreover, mid 2009, the recruitment process of in-hospital pharmacy data (including intravenous chemotherapy data) was still going on. Availability of cytostatics data was dependent on when and in which hospital the patient was treated and whether there was access to data from the in-hospital pharmacy in that specific time period. Recruitment of in-hospital pharmacies supplying the hospitals in the ECR-PHARMO region to obtain information on specific type of cytostatics administered intravenously was for about 45% complete in the study period 1998-2006. In this manuscript, a description of the data becoming available after linkage of two existing databases, and the most common categories of cytostatics per cancer type were shown. For a specific study using these data, one could present the various cancer treatments by tumour stage or stratify treatment regimens in first, second and third line therapy as was performed in a previous study in breast cancer patients[25].

The availability to select a cancer-free control group using data from the PHARMO RLS enables comparative studies between cancer patients and their cancer-free controls that would not be possible if there were only data on cancer patients. For example, the controls can be used to compare the rate of adverse events in cancer patients following cancer treatment with the rate of similar adverse events found in the general population as identified from the controls. These comparisons are of major importance as they allow quantification of the occurrence of adverse effects and accompanying risk factors.

Finally, additional information on quality of life measurements, information on health beliefs or health behaviours, psychological measurements, detailed patient characteristics, tumour biomarkers, disease progression and diagnostics not standard collected via the ECR or the PHARMO RLS can be collected additionally via medical files or questionnaires by going back to the original data sources or the patient.

In conclusion, the results of our study show that the linkage of data from the ECR and the PHARMO RLS is feasible and accurate; yielding a new database that facilitates broader research possibilities. The size of the cohort is still relatively limited and expansion is needed to facilitate the study of more rare cancers. However, it offers a unique opportunity for detailed pharmacoepidemiologic cancer-related treatment and outcomes research, eventually allowing improvement in future patient care.

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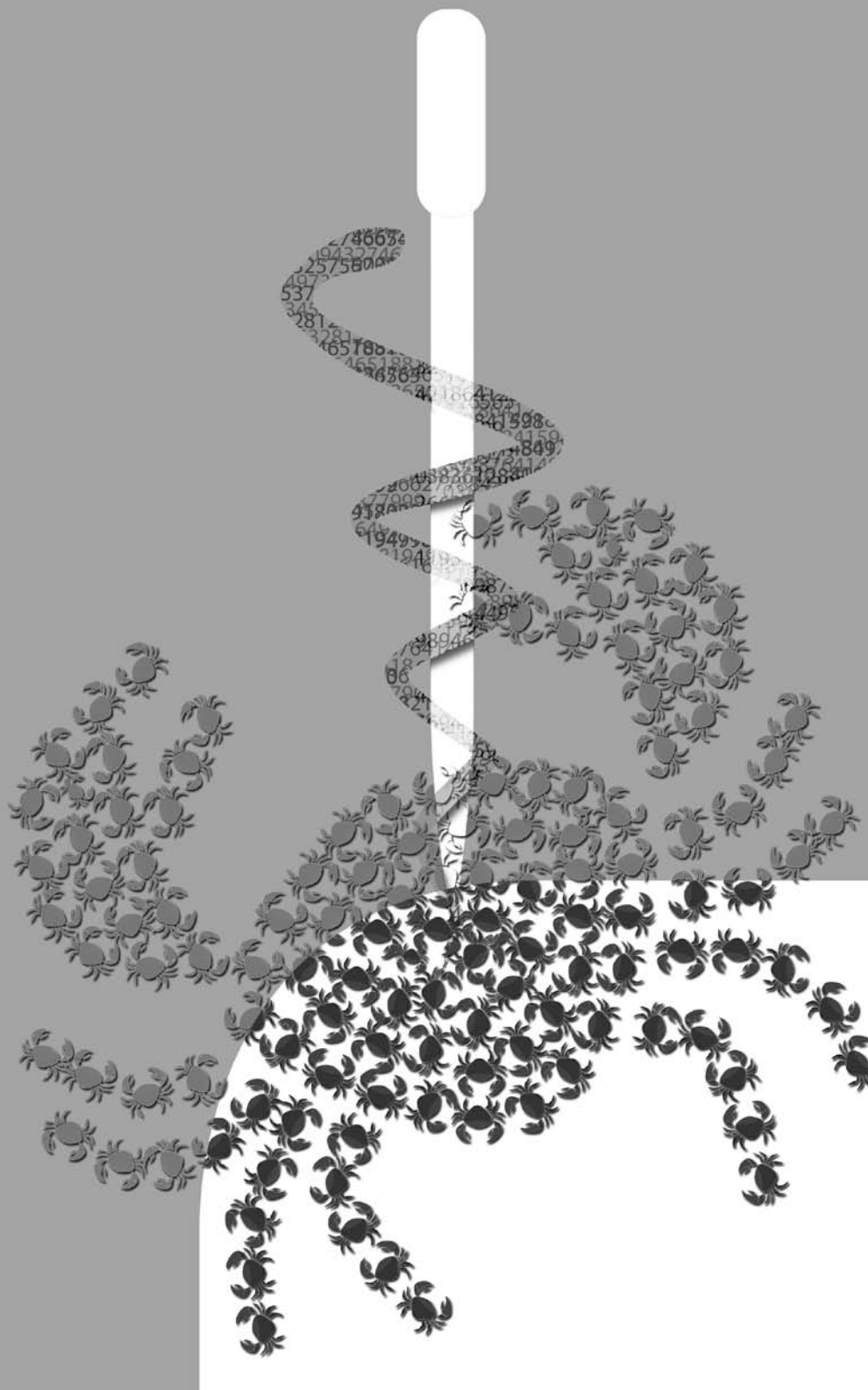

Substantial increase in the use of adjuvant systemic treatment for early stage breast cancer reflects changes in guidelines in the period 1990-2006 in the southeastern Netherlands

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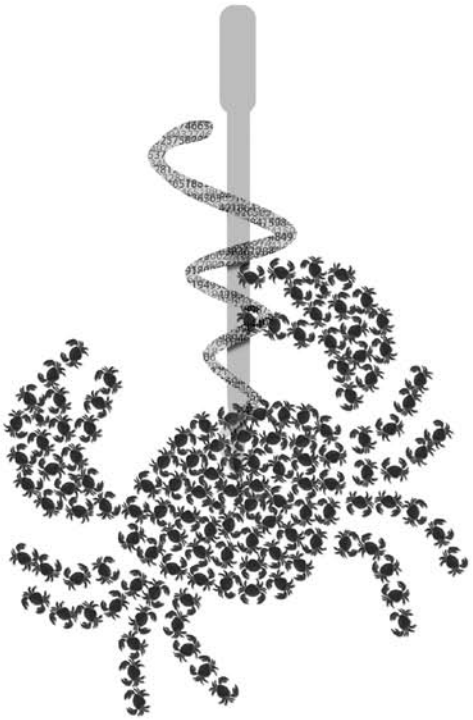

Abstract

Background:
Adjuvant systemic treatment for early stage breast cancer patients is focused on cure and the prevention of relapse.

Objectives:
This study evaluated trends in adjuvant systemic treatment among breast cancer patients and analysed the factors on which treatment choice was based.

Methods:
Patients diagnosed with early stage breast cancer in 1990-2006 were selected from the registry of the Eindhoven Cancer Registry (n=8,261). The probability of receiving therapy was determined per characteristic for the periods 1990-1997, 1998-2001 and 2002-2006, separately.

Results:
The use of adjuvant systemic treatment increased from 37% in 1990-1997 to 53% in 2002-2006. In 1990-1997, the probability of receiving chemotherapy was mainly determined by age and nodal status, while from 1998 onwards, tumour size, grade and hormone receptor status were also associated. The use of hormonal therapy was mainly determined by receptor status, in addition to age, nodal status, tumour size and grade. Marked differences were observed between hospitals in the adoption of adjuvant systemic treatment for node-negative patients.

Conclusions:
The use of adjuvant systemic treatment for breast cancer increased significantly in the period 1990-2006. In 1990-1997, treatment choice was mainly determined by age and nodal status, while from 1998 onwards, hormone receptor status, tumour size and grade were also considered. Overall, the likelihood of receiving chemotherapy remained strongly dependent of age.

Introduction

As the majority of breast cancers are diagnosed at an early stage,[1] treatment is focused on cure and the prevention of relapse. Adjuvant chemotherapy and hormonal therapy have proven to be effective in preventing or delaying relapses and increasing survival in patients with early stage breast cancer.[2-4] Therefore, these therapies have become part of the treatment plan of many of these patients. Based on results from clinical trials and reviews, the guidelines for adjuvant systemic treatment have evolved over time and strategies have become more tumour and patient specific than ever before.[5, 6]

Rising trends in the actual use of chemotherapy and hormonal therapy among breast cancer patients have been observed in the USA, regardless of lymph node and oestrogen receptor status.[7, 8] Women with node-positive tumours and younger women were more likely to receive chemotherapy than women with node-negative tumours and older women.[7, 8] Adjuvant systemic treatment for older women usually consisted of hormonal therapy alone and was given irrespective of the oestrogen receptor status of their tumours.[7]

Previous studies on factors influencing the choice of adjuvant systemic treatment in clinical practice found that increasing age decreased the likelihood of receiving chemotherapy[8-10], that patients with a large tumour, positive lymph node status and negative hormone receptor status were more likely to receive chemotherapy[8, 9, 11] and that women with a positive hormone receptor status more often received hormonal therapy[10, 11].

This study was undertaken to assess the extent to which adjuvant systemic treatment patterns among women with early stage breast cancer have changed from 1990 through 2006 in the southeastern part of the Netherlands. Special attention was paid to the independent factors that played a role in the choice of treatment during three different time periods in which major changes in the guidelines occurred.

Methods

The Eindhoven Cancer Registry (ECR) is a population-based registry, maintained by the Comprehensive Cancer Centre South (CCCS), and records data on all patients newly diagnosed with cancer in the southeastern part of the Netherlands, an area with now 2.4 million inhabitants (about 15% of the Dutch population). This population-based registry is notified by six pathology departments, ten community hospitals and two radiotherapy institutes. Registration takes place around six months after diagnosis. Trained registry personnel actively collect data on diagnosis, staging and treatment from the medical records after notification by pathologists and medical registration offices. The infrastructure of, and good access to, Dutch health care facilities, together with the notification procedures used, have made it possible to establish cancer registries with a completeness exceeding 95%.[12]

All patients diagnosed with a breast tumour, defined as C50.0–C50.6 according to ICD-O-3, in the period 1990–2006 were selected from the ECR. Only patients diagnosed with early stage breast cancer (stage I-IIIa) according to the International Union Against Cancer (UICC) TNM Classification of Malignant Tumours[13] were included in the study cohort.
Due to major changes in the Dutch guidelines for adjuvant systemic treatment in breast cancer in 1998 and 2002,[14, 15] characteristics of the patients included in the study cohort were shown for the periods 1990–1997, 1998–2001 and 2002–2006, separately. Age at diagnosis was classified into five groups: ≤ 35, 36-49, 50-59, 60-69 and ≥ 70 years. The following tumour characteristics were recorded: tumour size (≤1.0 cm, 1.1-2.0 cm, 2.1-5.0 cm and > 5.0 cm), lymph node status (positive or negative), histologic tumour grade (well differentiated (low grade), moderately differentiated (intermediate grade) and poorly or undifferentiated (high grade)) and oestrogen receptor (ER) and progesterone receptor (PR) status (positive or negative). Moreover, the following treatments that patients received after diagnosis were defined: chemotherapy (yes/no), hormonal therapy (yes/no), radiation therapy (yes/no), breast surgery (breast-conserving surgery or mastectomy) and combinations of the aforementioned therapies. Serious co-morbidity was recorded according to a slightly modified version of the Charlson classification[16] with classification based on the number of co-morbidities at time of diagnosis (none, 1, ≥ 2). An indicator of socio-economic status was provided at aggregated level for each postal code as described before.[17] Socio-economic status was categorized in high, intermediate and low and postal codes of care-providing institutions, such as nursing homes, were assigned to a separate category. Hospital of treatment was coded 1 to 7, including in this study only patients that were treated at the seven largest hospitals in the ECR area.

Analyses

Patient and tumour characteristics are displayed according to period of diagnosis. Trends in the distribution of the characteristics across the three periods (1990–1997, 1998–2001 and 2002–2006) were evaluated by p-value for linear trend computed by univariate logistic regression analyses, by categorizing the diagnostic periods and characteristics as ordinal variables. Distribution of the adjuvant systemic treatment (chemotherapy only, hormonal therapy only, both chemotherapy and hormonal therapy, or any adjuvant systemic treatment) are shown according to lymph node status, age and year of diagnosis. In these figures, age at diagnosis was classified into four groups: ≤ 35, 36-49, 50-69 and ≥ 70 years based on the Dutch breast cancer treatment guidelines.[14] The probability of receiving chemotherapy or hormonal therapy was determined per tumour and patient characteristic and presented by period of diagnosis. Since the parameter under study (receiving adjuvant systemic treatment) was not a rare event, odds ratios are not good approximations of probability ratios (risk ratios or prevalence ratios), as these overestimate the probability.[18] Probability ratios were therefore computed by SAS Proc Genmod using a modified Poisson regression approach. The following variables, which are considered to likely affect the use of adjuvant systemic treatment in breast cancer patients, were included in the model: age, tumour size, lymph node status, histologic tumour

grade, hormone receptor status, non-systemic cancer therapies, number of co-morbidities, socio-economic status and hospital of treatment. Difference in the probability of receiving adjuvant systemic treatment within a characteristic was assessed by the chi-square test using Proc Genmod, while adjusting for the other characteristics. Variation in administration of any adjuvant systemic treatment in the seven hospitals was determined over time. Results in the Tables are presented by period of diagnosis (1990-1997, 1998-2001 and 2002-2006) and in the Figures by year of diagnosis. For all analyses the SAS/STAT® statistical software (SAS system 8.2, SAS Institute, Cary, NC) was used.

Results

Table 1 lists the patient and tumour characteristics of the 8,261 women with early stage breast cancer included in the study, according to period of diagnosis. The use of adjuvant systemic treatment, irrespective of the type, increased from 37% in 1990-1997 to 51% in 1998-2001 and 53% in 2002-2006 (p for trend < 0.0001). The mean age at diagnosis was similar for all three periods (58, 59, and 58 years, respectively). Size of the breast tumours at diagnosis decreased significantly over time (p for trend < 0.0001). When not taking into account the large proportion of patients with an unknown histologic tumour grade or hormone receptor status, the proportion of patients with a well-differentiated tumour increased from 14% in 1990-1997 to 32% in 2002-2006, while the percentage of women with ER- and/or PR-positive tumours was stable over time, with 85% in 1990-1997 and 84% in 2002-2006. The percentage of women with breast-conserving surgery and radiation therapy increased, while the percentage of women with mastectomy, with or without radiation therapy, decreased (p for trend < 0.0001). Breast cancer therapy combinations including systemic therapy increased significantly over time (p for trend < 0.0001).

Table 1. Distribution of patient and tumour characteristics of women with early stage breast cancer, according to period of diagnosis

Characteristics	Period of diagnosis			
	1990-1997 (N=3,281) %	1998-2001 (N=2,034) %	2002-2006 (N=2,946) %	*p*-value for linear trend
Age				0.960
≤ 35 years	4	3	3	
36-49 years	25	24	26	
50-59 years	25	25	27	
60-69 years	25	23	22	
≥ 70 years	21	26	22	

Characteristics	Period of diagnosis 1990-1997 (N=3,281) %	1998-2001 (N=2,034) %	2002-2006 (N=2,946) %	*p*-value for linear trend
Tumour size				<.0001
≤1.0 cm	15	21	19	
1.1-2.0 cm	42	43	44	
2.1-5.0 cm	40	33	34	
> 5.0 cm	3	3	3	
Lymph node status				0.434
Positive	37	39	38	
Negative	59	58	58	
Unknown	4	3	4	
Histologic tumour grade				<.0001
Well	5	14	26	
Moderate	15	24	36	
Poor	15	20	20	
Unknown	65	42	18	
Hormone receptor status				<.0001
ER+ and/or PR+	60	67	80	
ER- and PR-	11	12	16	
Unknown	29	21	4	
Non-systemic cancer therapies				<.0001
BCS alone	2	4	3	
BCS and RT	51	57	62	
Mastectomy alone	29	26	22	
Mastectomy and RT	16	12	10	
Other/none/unknown	3	2	3	
Therapy				<.0001
S	23	16	10	
S+RT	40	33	36	
S+RT+ST	28	36	36	
S+ST	8	14	15	
ST	1	1	2	
Other/none/unknown	0	0	1	

Characteristics	Period of diagnosis 1990-1997 (N=3,281) %	1998-2001 (N=2,034) %	2002-2006 (N=2,946) %	*p*-value for linear trend
Number of co-morbidities				<.0001
None	48	61	56	
1	15	22	21	
≥ 2	5	10	12	
Unknown	33	7	11	
Socio-economic status				0.038
High	30	29	31	
Intermediate	38	40	41	
Low	28	26	23	
Institutionalized (nursing homes)	4	4	4	
Unknown	0	0	2	
Hospital of treatment				0.805
1	14	15	14	
2	12	11	11	
3	17	18	15	
4	6	5	7	
5	15	16	18	
6	13	13	13	
7	23	22	22	

ER: Oestrogen receptor; PR: Progesterone receptor; BCS: Breast-conserving surgery; RT: Radiation therapy; S: surgery; ST: systemic therapy

Figure 1a-1d and 2a-2d present the time trends in adjuvant systemic treatment by age category and year of diagnosis for women with early stage breast cancer with positive nodes (Figure 1) or negative nodes (Figure 2), excluding 298 patients of whom information on lymph node status was not available. Among patients ≤35, 36-49 and 50-69 years with node-positive breast cancer, the percentage receiving both hormonal therapy and chemotherapy increased over time, being 47%, 67% and 37%, respectively in 2006. Of the patients of 70 years and older, less than 2% received chemotherapy. For node-negative patients, the percentage receiving any adjuvant systemic treatment increased for all age groups from 1996 onwards and seemed to stabilize around 2000 for patients 50 years and older with approximately 23% usage, and around 2002 for patients younger than 50 years with approximately 44 % usage for patients 36-49 years and approximately 83% usage for patients ≤35 years. None of the node-negative patients aged ≥ 70 years received chemotherapy in the period 1990-2006.

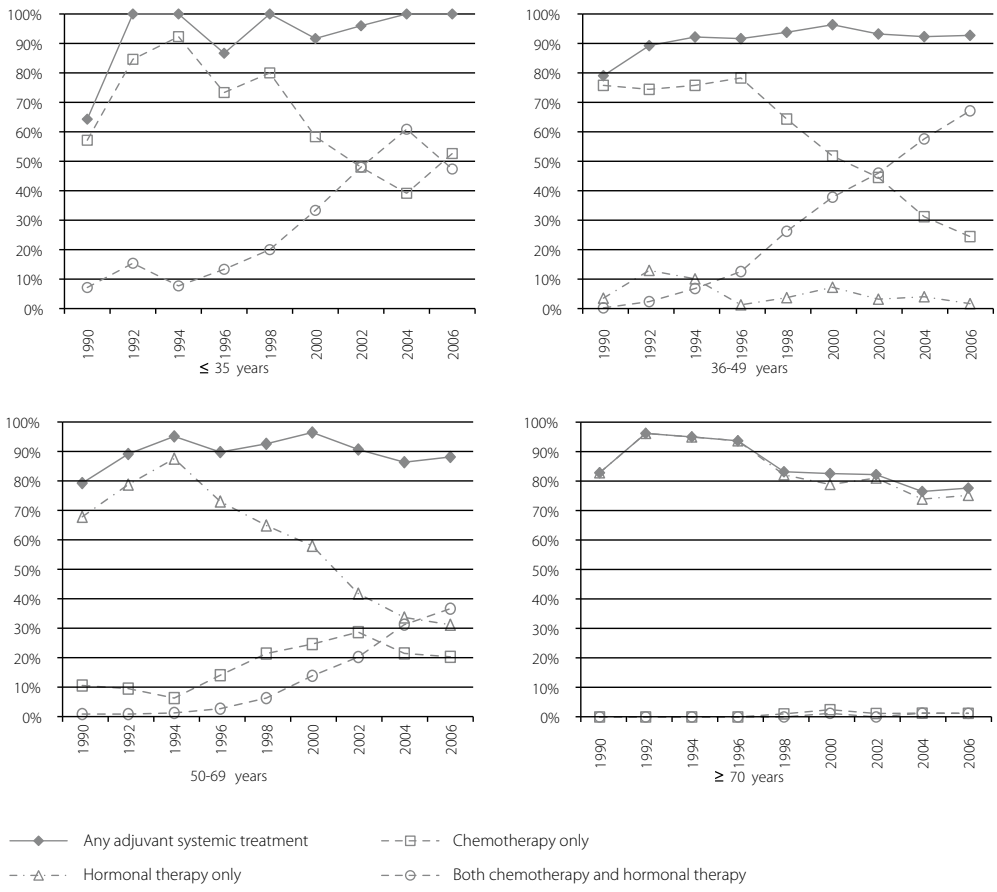

Figure 1a-1d. Proportion of women with early stage node-positive breast cancer receiving adjuvant systemic treatment, by age and year of diagnosis

Chemotherapy, Hormonal therapy and Both are mutually exclusive, Any adjuvant systemic treatment is the sum of the three aforementioned; Age categories are based on the Dutch breast cancer treatment guidelines[14].

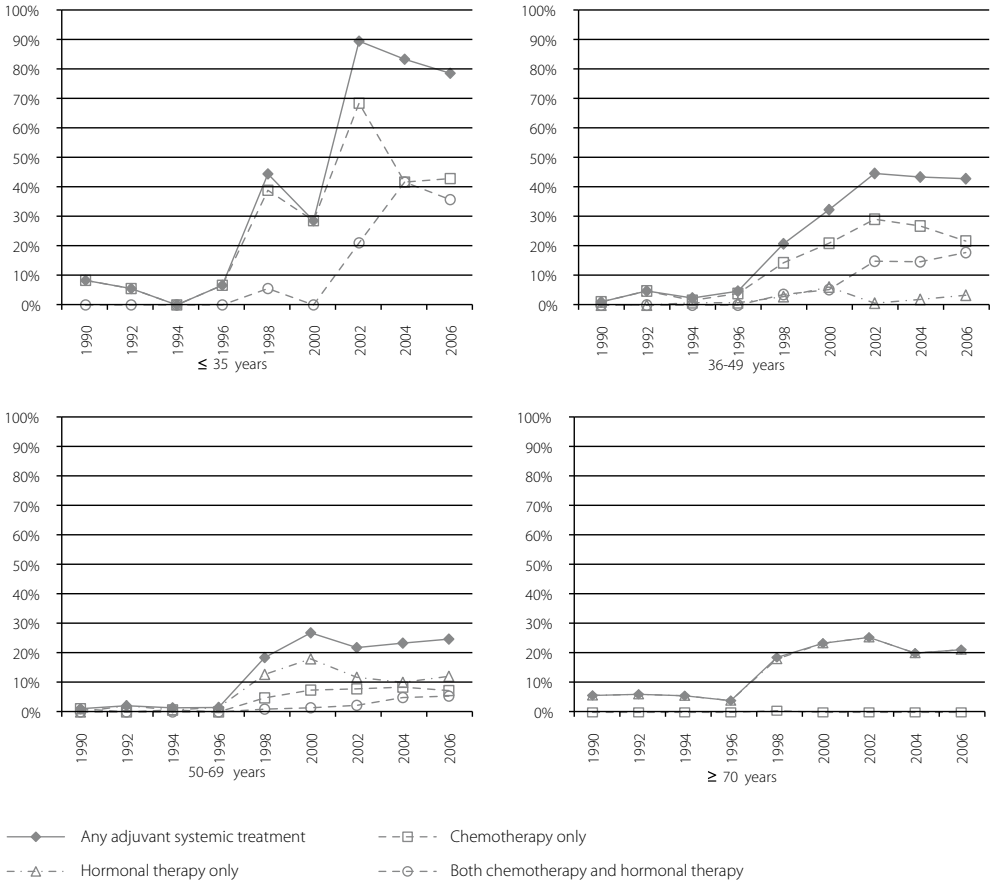

Figure 2a-2d. Proportion of women with early stage node-negative breast cancer receiving adjuvant systemic treatment, by age and year of diagnosis

Chemotherapy, Hormonal therapy and Both are mutually exclusive, Any adjuvant systemic treatment is the sum of the three aforementioned; Age categories are based on the Dutch breast cancer treatment guidelines[14].

The independent predictors of the probability of receiving chemotherapy changed over time, as presented in Table 2.

Table 2. Probability of receiving adjuvant chemotherapy* for women diagnosed with early stage breast cancer by tumour and patient characteristics, according to period of diagnosis

	1990-1997		1998-2001		2002-2006	
Characteristics	**PRadj**	**(95% CI)**	**PRadj**	**(95% CI)**	**PRadj**	**(95% CI)**
Age						
≤ 35 years	1	-[1]	1	-[1]	1	-[1]
36-49 years	0.92	(0.81-1.1)	1.2	(0.95-1.5)	0.94	(0.82-1.1)
50-59 years	0.24	(0.19-0.31)	0.68	(0.53-0.86)	0.66	(0.57-0.76)
≥ 60 years**	0.01	(0.00-0.02)	0.13	(0.09-0.19)	0.14	(0.11-0.18)
Tumour size						
≤ 1.0 cm	1	-	1	-[2]	1	-[1]
1.1 – 2.0 cm	1.2	(0.89-1.6)	1.5	(1.1-1.9)	1.8	(1.4-2.1)
2.1 -5.0 cm	1.2	(0.88-1.6)	1.7	(1.3-2.2)	2.2	(1.8-2.6)
> 5.0 cm	1.2	(0.86-1.7)	2.1	(1.5-2.9)	2.3	(1.8-3.0)
Lymph node status						
Negative	1	-[1]	1	-[1]	1	-[1]
Positive	26	(17-40)	3.6	(3.0-4.3)	2.3	(2.1-2.6)
Histologic tumour grade						
Well	1	-	1	-[1]	1	-[1]
Moderate	1.1	(0.76-1.6)	1.3	(0.97-1.7)	1.4	(1.2-1.7)
Poor	1.3	(0.98-2.0)	1.7	(1.3-2.3)	2.2	(1.8-2.5)
Unknown	1.2	(0.88-1.7)	1.3	(0.96-1.7)	1.6	(1.3-1.9)
Hormone receptor status						
ER+ and/or PR+	1	-	1	-[1]	1	-[1]
ER- and PR-	1.2	(0.99-1.4)	2.1	(1.8-2.4)	1.6	(1.4-1.7)
Unknown	1.1	(0.96-1.2)	0.61	(0.48-0.77)	0.82	(0.57-1.2)

PRadj: Probability Ratio, adjusted for age, tumour size, lymph node status, histologic tumour grade, hormone receptor status, non-systemic cancer therapies, number of co-morbidities, socio-economic status and hospital of treatment; 95% CI: 95% Confidence interval; ER: Oestrogen receptor; PR: Progesterone receptor; * Chemotherapy alone, or in combination with hormonal therapy; ** Patients aged 60-69 years and ≥ 70 years have been grouped together due to low number of patients older than 70 years receiving chemotherapy; Due to low numbers, patients with tumour size 'unknown', and lymph node status 'unknown' were deleted from the analysis (N=3); [1]p<0.0001, [2]p=0.0001-0.001: Statistically significant difference in the probability of receiving chemotherapy within the categories of that specific characteristic

Decrease in the use of chemotherapy with advancing age was seen in 1990-1997 as well as in 1998-2001 and 2002-2006. In the period 1990-1997, positive lymph node status and younger age were the only significant predictors for the use of chemotherapy. From 1998 onwards, increasing tumour size, poor tumour differentiation and negative hormone receptor status were

additional factors that were positively associated with the probability of receiving chemotherapy, taking into account non-systemic cancer therapies (breast-conserving surgery, mastectomy and radiation therapy), number of co-morbidities, socio-economic status and hospital of treatment.

Table 3. Probability of receiving adjuvant hormonal therapy* for women diagnosed with early stage breast cancer by tumour and patient characteristics, according to period of diagnosis

	1990-1997		1998-2001		2002-2006	
Characteristics	**PRadj**	**(95% CI)**	**PRadj**	**(95% CI)**	**PRadj**	**(95% CI)**
Age						
≤ 35 years	1	-[1]	1	-[1]	1	-[2]
36-49 years	1.2	(0.53-2.6)	1.5	(0.82-2.6)	0.90	(0.73-1.1)
60-69 years	6.7	(3.2-14)	2.7	(1.5-4.7)	0.92	(0.75-1.1)
50-59 years	8.1	(3.8-17)	3.3	(1.9-5.8)	1.0	(0.83-1.3)
≥ 70 years	9.3	(4.4-20)	3.3	(1.9-5.9)	1.1	(0.88-1.3)
Tumour size						
≤ 1.0 cm	1	-	1	-[1]	1	-[1]
1.1 – 2.0 cm	1.2	(1.0-1.4)	1.5	(1.2-1.8)	1.7	(1.4-2.1)
2.1 -5.0 cm	1.2	(0.99-1.4)	1.5	(1.3-1.9)	2.3	(1.9-2.7)
> 5.0 cm	1.2	(0.99-1.5)	1.9	(1.4-2.4)	2.2	(1.7-2.7)
Lymph node status						
Negative	1	-[1]	1	-[1]	1	-[1]
Positive	35	(25-49)	3.7	(3.2-4.3)	2.9	(2.6-3.2)
Unknown	18	(12-27)	2.3	(1.7-3.1)	2.5	(2.0-3.2)
Histologic tumour grade						
Well	1	-	1	-[1]	1	-[1]
Moderate	1.1	(0.94-1.3)	1.3	(1.1-1.5)	1.3	(1.1-1.4)
Poor	1.1	(0.95-1.3)	1.6	(1.3-1.9)	1.7	(1.5-1.9)
Unknown	1.1	(0.94-1.3)	1.2	(1.0-1.4)	1.2	(1.0-1.4)
Hormone receptor status						
ER+ and/or PR+	1	-[2]	1	-[1]	1	-[1]
ER- and PR-	0.84	(0.74-0.96)	0.2	(0.14-0.30)	0.06	(0.04-0.10)
Unknown	0.94	(0.86-1.0)	0.6	(0.47-0.63)	0.45	(0.33-0.61)

PRadj: Probability Ratio, adjusted for age, tumour size, lymph node status, histologic tumour grade, hormone receptor status, non-systemic cancer therapies, number of co-morbidities, socio-economic status and hospital of treatment; 95% CI: 95% Confidence interval; ER: Oestrogen receptor; PR: Progesterone receptor; * Hormonal therapy alone, or in combination with chemotherapy; Due to low numbers, patients with tumour size 'unknown' were deleted from the analysis (N=2); [1]p<.0001, [2]p=0.01-0.05: Statistically significant difference in the probability of receiving hormonal therapy within the categories of that specific characteristic

Univariate analyses showed that in all three periods, patients with co-morbidity compared to patients without co-morbidity and patients with a low socio-economic status, or who were institutionalized at time of diagnosis, compared to patients with a high socio-economic status, were less likely to receive chemotherapy. Moreover, univariate analyses showed a difference in the administration of chemotherapy between the seven hospitals. However, these differences were no longer significant after adjustment for potential confounders in the multivariate analyses.

Results of the multivariate analyses of the characteristics that influence the probability to receive hormonal therapy are shown in Table 3. The use of hormonal therapy in the period 1990-1997 was determined by the presence of positive lymph nodes, increasing age and positive hormone receptor status. In the period 1998-2001, additional predictors of the probability to receive hormonal therapy were increasing tumour size and poor differentiation of the tumour. In 2002-2006 age had become a less important factor in the choice of hormonal therapy use compared to the two other periods and a positive hormone receptor status became the most important factor determining hormonal therapy use. Non-systemic cancer therapies, the number of co-morbidities, socio-economic status and hospital of treatment were also included in the multivariate model but showed no significant relation with the use of hormonal therapy.

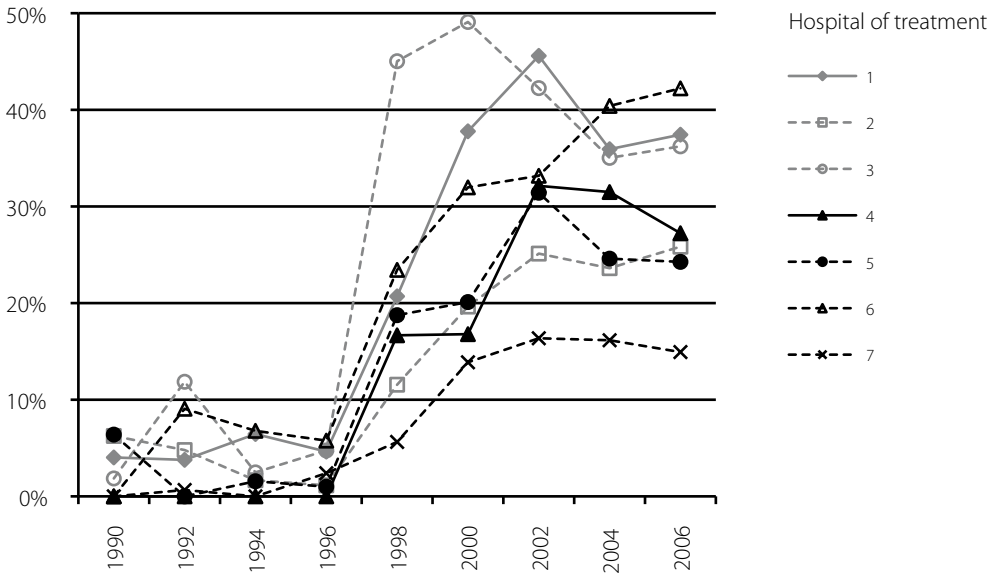

Figure 3. Proportion of women with early stage node-negative breast cancer receiving adjuvant systemic treatment (chemotherapy and/or hormonal therapy), by hospital of treatment and year of diagnosis

There were no large differences observed between the hospitals in the administration of any adjuvant systemic treatment for early stage node-positive breast cancer patients in the period 1990-2006. For node-negative breast cancer patients, marked differences were seen between the seven hospitals of treatment (see Figure 3). Node-negative breast cancer patients treated in hospitals which were early adopters of the guidelines (hospital 1, 3 and 6) were more likely to receive any adjuvant systemic therapy compared with patients treated in hospital 7, which was a late adopter of the treatment guidelines. This was seen in period 1998-2001 as well as in period 2002-2006, after adjustment for potential confounders (PR 2.5; 95% CI 1.7-3.6 and PR 1.5; 95% CI 1.3-1.9, respectively).

Discussion

The use of adjuvant systemic treatment for patients with early stage breast cancer increased significantly over time, from 37% in the period 1990-1997, to 53% in 2002-2006. This increase differed according to patients' age and tumour characteristics. In the earlier years (1990-1997) age and lymph node status were the most important determinants in the choice of adjuvant systemic treatment, while from 1998 onwards the decision became increasingly dependent on the hormone receptor status, tumour size and histologic tumour grade, which is in accordance with the incorporation of these factors in the treatment guidelines.[14] While several studies have demonstrated the impact of guidelines on the use of adjuvant systemic treatment in clinical practice,[7, 8, 19-22] this study is the first to quantify relative effect estimates by calculating adjusted probability ratios in three subsequent time-periods, characterised by major changes in treatment guidelines.

During the whole study period, age remained the most important factor in the decision whether or not a patient should receive chemotherapy. Like in previous published studies, the use of chemotherapy, alone or in combination with hormonal therapy, decreased with increasing age.[3, 7-9, 20, 21, 23-26] The fact that older women are less likely to be treated with adjuvant chemotherapy may be explained by many factors, including co-morbidities and lack of evidence for the benefit of chemotherapy for women aged 70 years and older.[3, 7, 8, 10, 20, 21, 23, 27, 28]

The use hormonal therapy, however, was much less dependent of age: in the period 2002-2006 age was no longer a significant predictor of the use of hormonal therapy, which is in accordance with the findings of other studies.[25, 29] Over the years, the hormone receptor status became the most important factor to determine whether or not a patient should receive therapy. This is in line with the guidelines, recommending only hormonal therapy for patients with a breast tumour with a positive hormone receptor status from 1998 onwards.[14]

Next to the patient and tumour characteristics shown in Table 2 and 3, which are incorporated in the current guidelines, several other factors that may influence the choice of adjuvant systemic treatment in clinical practice, such as co-morbidity, socio-economic

status and hospital of treatment, have been taken into account in this study. In our study, co-morbidity was no longer associated with the use of adjuvant systemic treatment after adjusting for potential confounders, while previous studies found a small, though significant, decrease in the likelihood of receiving chemotherapy when co-morbidity was present.[3, 8, 9] For node-negative breast cancer patients, this study found marked differences in the use of adjuvant systemic treatment between the seven community hospitals in the southeastern part of the Netherlands. The observed pattern illustrates that there have been early and late adopters of the treatment guidelines, despite the coordinating role of the CCCS in the diffusion of the guidelines in this area. Whether this variation is due to the physicians based in these hospitals or other hospital characteristics could not be determined from the data used in this study.

HER2/neu is a tumour marker that plays a role in predicting the response to specific adjuvant systemic treatments for women with breast cancer.[30] No trend could be evaluated for this tumour characteristic as HER2/neu status was not available in the registry in all three time periods (1990-1997, 1998–2001 and 2002–2006). In the near future, HER2/neu overexpression should be included in studies analysing factors associated with the use of adjuvant systemic treatment for patients with early stage breast cancer, as more clinicians will be considering it when deciding which adjuvant systemic treatment options should be offered to their patients.

In conclusion, trends in adjuvant systemic treatment over a large period of time (1990-2006) showed that treatment with hormonal therapy and chemotherapy increased over time, especially for patients with node-negative breast cancer. In the earlier years (1990-1997) the probability of receiving adjuvant systemic treatment was mainly determined by age and lymph node status, while from 1998 onwards, hormone receptor status, tumour size and histologic tumour grade were also taken into account when deciding if and which systemic therapy options should be offered to a patient. Patient's age remained an important factor when deciding on the use of chemotherapy and, as is reflected by the marginal use in patients ≥70 years, most clinicians do not consider it to be an effective treatment option for their elderly patients. Moreover, hospital variation showed that there were early and late adopters of the treatment guidelines in clinical practice, despite the coordinating role of the CCCS in the diffusion of the guidelines in southeastern part of the Netherlands.

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Major changes in chemotherapy regimens administered to breast cancer patients during 2000-2008

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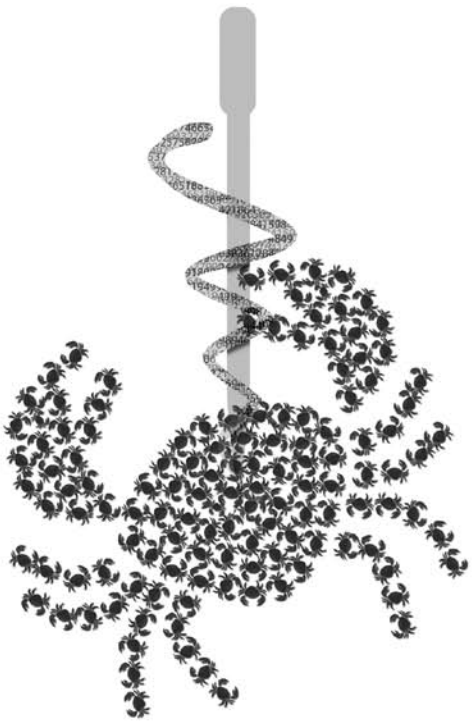

Abstract

Background:
There is little information available on the patterns of chemotherapy regimens used in breast cancer patients in daily practice.

Objectives:
To determine trends in type of chemotherapy regimens administered to early stage or metastatic breast cancer patients.

Methods:
Breast cancer patients in the period 2000-2008 who received chemotherapy were selected from the Eindhoven Cancer Registry, including data on all newly diagnosed cancer patients in the southeastern Netherlands. Those included were linked to the PHARMO Record Linkage System, including data on, among other things, in- and outpatient drug use. First and subsequent chemotherapy regimens were classified based on the received combinations. Trends in the distribution of adjuvant chemotherapy regimens (for early stage breast cancer) and palliative chemotherapy regimens (for metastatic breast cancer) were determined and stratified by Her2/neu status when possible.

Results:
In this study, 422 patients diagnosed with early stage breast cancer received adjuvant chemotherapy. The use of CMF (cyclophosphamide, methotrexate and 5-fluorouracil) decreased from 90% in 2000 to almost none since 2005. Administration of anthracyclines (without taxanes) increased from 4% in 2000 to 94% in 2005, but decreased to 60% in 2008, being replaced by both trastuzumab and taxanes (with or without anthracyclines). Among the 82 breast cancer patients who received palliative chemotherapy at diagnosis or after breast cancer recurrence, the use of CMF and anthracyclines (without taxanes) decreased (0% and 15% in 2008, respectively), while the use of taxanes (with or without anthracyclines) increased (26% in 2008). Trastuzumab was used as palliative chemotherapy from 2003 onwards, with 22% of the metastatic breast cancer patients receiving trastuzumab containing regimens in 2008, and bevacizumab was administered since 2007 with 19% of the patients receiving bevacizumab containing regimens in 2008.

Conclusions:
Major changes have taken place in the chemotherapeutic treatment of patients with early and recurrent breast cancer. These changes reflect the key findings from large clinical trials, as incorporated in the Dutch guidelines.

Introduction

Treatment of breast cancer with chemotherapeutic agents is a rapidly evolving field which includes both the conventional agents that interfere with rapidly dividing cells as well as the targeted therapies that interfere with specific targeted molecules needed for carcinogenesis and tumour growth[1]. Adjuvant chemotherapy is administered to early stage breast cancer patients after local-regional treatment to improve survival by eliminating residual micrometastatic disease[2]. Neoadjuvant (preoperative) chemotherapy is increasingly applied in the last decade among patients with locally advanced breast cancer. Potential benefits are a greater likelihood of breast conserving surgery and the ability to predict the effectiveness of chemotherapy by evaluating the response of the primary tumour[3]. Palliative chemotherapy is administered to patients with metastatic breast cancer (at diagnosis or after distant breast cancer recurrence) to delay tumour progression and provide relief of symptoms[4].

In the last quarter of the previous century, treatment for early stage breast cancer included a combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) which demonstrated a reduced risk of breast cancer recurrence and death in women with operable node-positive breast cancer[5]. In the eighties, anthracycline-containing combinations were tested in the adjuvant setting, followed by taxanes in the nineties[2]. Overall, the taxane containing combinations are superior to anthracycline containing combinations which perform better than CMF. However, this superior effectiveness is often associated with more toxicity[2, 6-8]. Finally, in 2005, trastuzumab entered the adjuvant setting, after it had shown to be significantly improving disease free and overall survival in breast cancer patients whose tumours over-express Her2/neu[9]. Next to the chemotherapeutics approved for the treatment of early stage breast cancer, there are the agents such as capecitabine, vinorelbine and gemcitabine, or targeted therapies such as bevacizumab and lapatinib, that have been approved for the treatment of metastatic breast cancer[4].

Guidelines are provided to assist clinicians to determine which type of single agent or multidrug chemotherapy to use[10-12]. Little information is available in literature on the exact types of chemotherapeutics administered in daily practice, especially in the more recent years[13-15]. Investigating recent trends will help predict future developments and is useful for clinicians and policy makers to understand the speed in which new guidelines are adopted. Therefore, we determined the types and trend of use of chemotherapy regimens administered to patients with early stage or metastatic breast cancer.

Methods

Data Sources

Data were obtained from the Eindhoven Cancer Registry (ECR) linked on a patient-level to the PHARMO Record Linkage System (PHARMO RLS) covering an overlapping demographic region in the southeastern part of the Netherlands of approximately one million inhabitants. The construct and validity of the ECR-PHARMO cohort are described elsewhere.[16] The ECR is a population-based registry which is maintained by the Comprehensive Cancer Centre South and collates records on all newly diagnosed cancer patients in the southeastern part of the Netherlands. Trained registry personnel actively collect on site data on patient characteristics (e.g. co-morbidity at diagnosis), diagnosis, tumour staging, and treatment received directly after diagnosis (e.g. chemotherapy (yes/no), radiation therapy and type of surgery).

The PHARMO RLS is a large patient-centric data network including multiple linked observational databases designed for safety and outcomes research of drugs. Databases relevant for this study include complete longitudinal data obtained from hospital discharge records (Dutch Hospital Data: LMR), community pharmacies (out-patient) and in-hospital pharmacies (in-patient). Data on type of chemotherapy were obtained from the community and in-hospital pharmacy databases based on Anatomical Therapeutic Chemical (ATC) code L01. Data on oral agents were mainly obtained from the community pharmacies, while data on intravenously administered agents were extracted from the in-hospital pharmacies. As every hospital has its own way of documenting the administered type of chemotherapeutic agent, regimen and dosing, extracting of the electronic and non-electronic data was difficult and therefore, data were only available for a subpopulation of the ECR-PHARMO cohort.

Study population

The source population included all women registered in the ECR-PHARMO cohort diagnosed with breast cancer in the period January 1, 2000 to December 31, 2008. From this source population it was determined whether they received chemotherapy. Of the patients who received chemotherapy, data on specific types of chemotherapeutic agents administered was available for a sub-cohort. Patients included in this study cohort were followed from breast cancer diagnosis onwards and were censored at time of hospitalisation for cancer other than breast cancer (ICD-9-CM codes 140-230 excl. 174, 196, 197, 198 or 199), death, loss to follow-up in the PHARMO RLS, or end of study period (December 31, 2008), whichever occurred first.

Dutch guidelines of chemotherapy treatment for breast cancer

Up to 2005, the advised adjuvant chemotherapy regimens were CMF or anthracycline based regimens[11, 12]. From 2005 onwards, anthracycline based regimens alone or followed by taxanes were advised to Her2/neu negative patients and anthracyclines followed by

taxanes with trastuzumab for patients with Her2/neu overexpression[10]. For neoadjuvant therapy, the same regimens as for adjuvant chemotherapy were recommended[10]. For palliative chemotherapy, guidelines were less specific, with trastuzumab containing chemotherapies being recommended for patients with Her2/neu overexpression and otherwise CMF, anthracycline or taxanes based chemotherapy regimens[11, 12]. From 2007 onwards, bevacizumab was recommended in combination with paclitaxel in patients with metastatic breast cancer without Her2/neu overexpression who did not respond to anthracycline based regimens[17].

Chemotherapy regimens

Administered chemotherapies after breast cancer diagnosis were classified in regimens of use based on the received chemotherapy combinations and sequences. The regimens of chemotherapy used were classified as CMF, anthracycline based regimens (FEC: 5-fluorourcil, epirubicin, cyclophosphamide; AC: doxorubicin, cyclophosphamide; and FAC: 5-fluourouracil, doxorubicin, cyclophosphamide), taxane based regimens (TAC: docetaxel, doxorubicin, cyclophosphamide; taxane as single agent or taxane with anthracycline), trastuzumab containing regimens, bevacizumab containing regimens and other (single agents e.g. cyclophosphamide, capecitabine and vinorelbine). Adjuvant chemotherapy regimens were defined as chemotherapy regimens received by early stage breast cancer patients (stage I-III) after diagnosis up to an interruption between two chemotherapy regimens of more than 90 days. Of these patients it was determined whether they received neoadjuvant chemotherapy, defined as chemotherapy received before surgery. Palliative chemotherapy regimens were defined as regimens received by breast cancer patients who had metastatic disease at diagnosis (stage IV), or regimens received after an interruption of more than 90 days by patients who had early stage breast cancer at diagnosis assuming that these patients restarted chemotherapy due to a distant recurrence.

Her2/neu status

From 2005 onwards, Her2/neu overexpression has been recorded in the ECR. However, Her2/neu status of a breast tumour could not always be established. Moreover, for patients diagnosed with breast cancer before 2005, Her2/neu status was not registered and therefore unknown. Patients were defined as having a breast tumour with Her2/neu overexpression if the Her2/neu status was registered positive or if the Her2/neu status was unknown, but the patient received trastuzumab (presumably with a positive Her2/neu status). The remainder of the patients was classified in the group of Her2/neu status negative or unknown.

Analyses

The representativeness of the breast cancer patients for whom detailed chemotherapy data was available (the study cohort) was determined by comparing characteristics of these women with patients who did receive chemotherapy but for whom detailed

chemotherapy data was not available, by using the Chi-square test. Chi-square trend test was used to assess the changes in characteristics over time. Trends in the distribution of adjuvant and palliative chemotherapy regimens are shown according to year of administration of the regimens, including CMF, anthracyclines, taxanes, trastuzumab, bevacizumab and other cytostatics. The types of chemotherapy regimens (single agent or multidrug) administered as adjuvant or palliative chemotherapy were defined by Her2/neu status. Moreover, for adjuvant therapy, the proportion of patients receiving a specific chemotherapy combination were determined across four periods of time (2000-2002, 2003-2004, 2005-2006 and 2007–2008) and stratified by Her2/neu status, with those for Her2/neu overexpression presented from 2005 onwards as from that year on it had been recorded in the ECR. Data were analysed using SAS programs that are organised within SAS Enterprise Guide version 4.1 (SAS Institute Inc., Cary, NC, USA). Data management was conducted under UNIX using SAS version 9.1.

Results

There were 6,050 female breast cancer patients included in the linked ECR-PHARMO cohort during 2000-2008, of whom 1,847 (30.5%) received chemotherapy. For 453 (25%) of those patients, data on specific types of chemotherapeutic agents administered was available during follow-up. These patients did not differ significantly with respect to age, tumour stage and other therapies received compared to those without detailed chemotherapy data available (Table 1). The period of diagnosis, however, was different between both groups: detailed data on chemotherapy regimen was more likely to be available for patients diagnosed with breast cancer in the more recent years (> 2003). There were no substantial changes over time in the distribution of age, tumour stage, received surgery, radiotherapy or endocrine therapy (p for trend > 0.1).

Table 1. Characteristics of breast cancer patients treated with chemotherapy in the first year after diagnosis, by detailed data on regimen type available (yes/no)

	Patients treated with chemotherapy		
Characteristics at diagnosis	**Patient with no detailed chemotherapy data[1] available N=1,394 n (%)**	**Patients with detailed chemotherapy data[1] available N=453 n (%)**	**p-value**
Age			0.863
< 35 years	89 (6.4)	24 (5.3)	
35-49 years	601 (43.1)	197 (43.5)	
50-59 years	472 (33.9)	151 (33.3)	
60-69 years	201 (14.4)	72 (15.9)	
≥ 70 years	31 (2.2)	9 (2.0)	
Period of diagnosis			<.0001
2000-2002	423 (30.3)	87 (19.2)	
2003-2004	309 (22.2)	113 (24.9)	
2005-2006	308 (22.1)	137 (30.2)	
2007-2008	354 (25.4)	116 (25.6)	
Tumour stage			0.233
I	219 (15.7)	62 (13.7)	
II	824 (59.1)	256 (56.5)	
III	277 (19.9)	104 (23.0)	
IV	55 (3.9)	26 (5.7)	
unknown	19 (1.4)	5 (1.1)	
Therapy other than chemotherapy			
Surgery (yes)	1,352 (97.0)	434 (95.8)	0.222
Radiotherapy (yes)	1,046 (75.0)	339 (74.8)	0.932
Endocrine therapy (yes)	747 (53.6)	249 (55.0)	0.609

[1]Data on specific type of single agent or multidrug chemotherapy

Of the 453 breast cancer patients included in the study cohort, 422 were diagnosed with breast cancer stage I-III and received adjuvant chemotherapy after diagnosis. Of those, 9% received chemotherapy as a neoadjuvant treatment. This percentage increased during the study period, with none of the patients receiving neoadjuvant chemotherapy in the year 2000 and 16% in 2008. The distribution of the types of neoadjuvant chemotherapy administered was similar to the distribution of all adjuvant chemotherapies, therefore results are presented together with adjuvant administered chemotherapies.

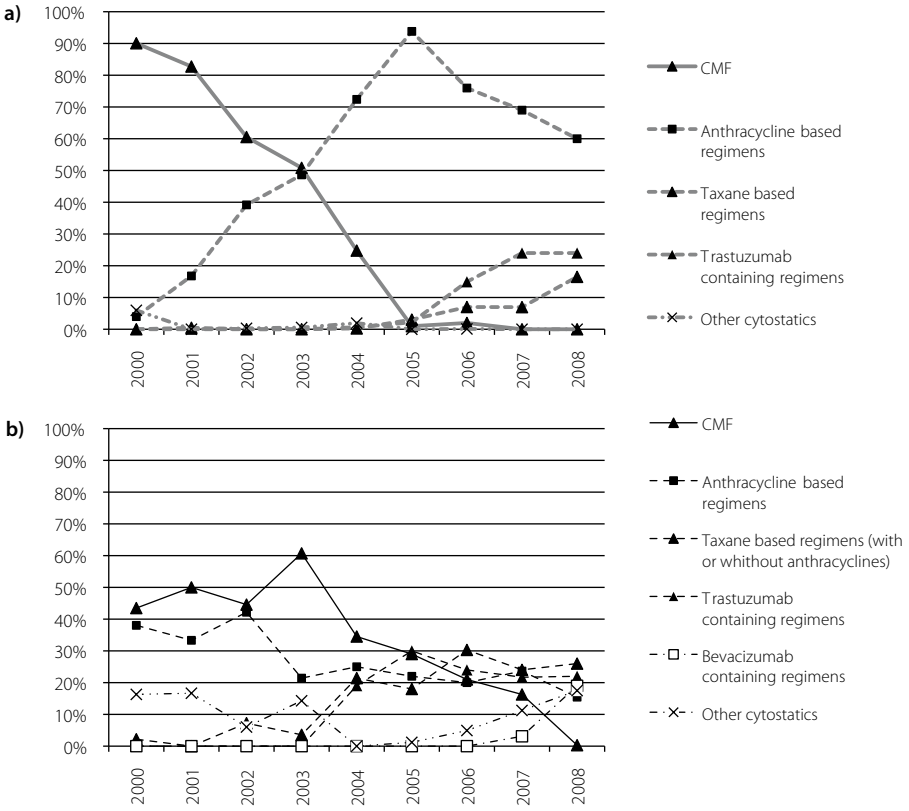

Figure 1. Trend in the distribution of breast cancer chemotherapy regimens in the southeastern Netherlands by a) adjuvant chemotherapy regimens and b) palliative chemotherapy regimens

CMF: cyclophosphamide, methotrexate, 5-fluorouracil

Table 2. Adjuvant and palliative chemotherapy regimens for the treatment of breast cancer in the period 2000-2008, by Her2/neu status

	Adjuvant chemotherapy				Palliative chemotherapy			
	Her2/neu positive N=58		Her2/neu negative or unknown N=364		Her2/neu positive N=24		Her2/neu negative or unknown N=58	
Type of chemotherapy regimen	**n**	**%**	**n**	**%**	**n**	**%**	**N**	**%**
CMF	1	1.7	56	15.4			1	1.7
Anthracycline based regimens	11	19.0	278	76.4			16	27.6
FEC alone	8	13.8	234	64.3			9	15.5
AC alone	3	5.2	37	10.2			1	1.7
FAC alone			6	1.6			1	1.7
Anthracycline followed by another cytostatic (regimen)[1]			1	0.3			5	8.6
Taxane based regimens	1	1.7	29	8.0	1	4.2	25	43.1
TAC alone	1	1.7	15	4.1				
Docetaxel alone			2	0.5			7	12.1
Paclitaxel alone							3	5.2
Anthracycline and taxane			11	3.0			10	17.2
Taxane followed by another cytostatic (regimen)[1]			1	0.3	1	4.2	5	8.6
Trastuzumab containing regimens	43	74.1			22	91.7		
Trastuzumab alone					9	37.5		
Anthracycline[2] followed by trastuzumab	10	17.2			4	16.7		
Anthracycline[2] followed by taxane with trastuzumab	23	39.7						
Taxane[3] followed by / in combination with trastuzumab	10	17.2			9	37.5		
Bevacizumab containing regimens					1	4.2	6	10.3
Other cytostatics[4]	2	3.4	1	0.3			10	17.2

CMF: cyclophosphamide, methotrexate, 5-fluorouracil; FEC: 5-fluorouracil, epirubicin, cyclophosphamide; AC: doxorubicin, cyclophosphamide; FAC: 5-fluorouracil, doxorubicin, cyclophosphamide; TAC: docetaxel, doxorubicin, cyclophosphamide; [1]another cytostatic (regimen) e.g. CMF, capecitabine or vinorelbine; [2]Antracycline= anthracycline based regimens (FEC, AC, FAC) or single agent (e.g. doxorubicin); [3]Taxane= taxane based regimens (TAC) or single agents (e.g. docetaxel, paclitaxel); [4]cytostatic monotherapy e.g. cyclophosphamide, capecitabine, vinorelbine.

In our study cohort there were 26 patients with breast cancer stage IV at diagnosis and of the breast cancer patients diagnosed with stage I-III, 56 patients restarted chemotherapy after three months. The types of chemotherapy regimens received by both groups were similar, although patients restarting chemotherapy received slightly more often an anthracycline plus taxane instead of an anthracycline alone. Results were presented together, resulting in 82 patients receiving palliative chemotherapy.

The use of CMF as adjuvant chemotherapy decreased from 90% in 2000 to almost none from 2005 onwards (Figure 1a). The use of anthracycline without taxanes increased from 4% in 2000 to 94% in 2005 and decreased from 2005 onwards to 60% in 2008. Both the use of trastuzumab containing regimens and taxane based regimens (with or without anthracyclines) increased from 2005 onwards to 24% and 16% respectively in 2008. For palliative administered regimens, trends in treatment were less straightforward (Figure 1b). The use of CMF and anthracycline based regimens decreased over time, while the use of taxane based regimens increased. Trastuzumab containing regimens were used as palliative chemotherapy from 2003 onwards and bevacizumab was administered as palliative treatment from 2007 onwards.

Of the 422 patients receiving adjuvant chemotherapy in the total study period, 58 patients (14%) were diagnosed with Her2/neu overexpression (Table 2). The majority of these patients (74%) received trastuzumab after anthracycline treatment and/or in combination with a taxane (paclitaxel or docetaxel). Patients who were diagnosed with a Her2/neu negative tumour or unknown Her2/neu status, mainly received FEC (64%). Of the 82 patients receiving palliative chemotherapy, 24 patients (29%) were diagnosed with Her2/neu overexpression. Almost all of these patients (92%) received trastuzumab containing regimens. Patients who were diagnosed with a Her2/neu negative tumour or unknown Her2/neu status mainly received taxane based regimens (43%). Additional analyses showed that of the 21 patients diagnosed with Her2/neu overexpression that were not yet treated with trastuzumab in the adjuvant setting, 86% did receive trastuzumab in the palliative setting. Of the Her2/neu negative patients treated with an anthracycline based regimen in the adjuvant setting and who had a distant recurrence during follow-up (N=30), the majority (73%) restarted chemotherapy with a taxane based regimen.

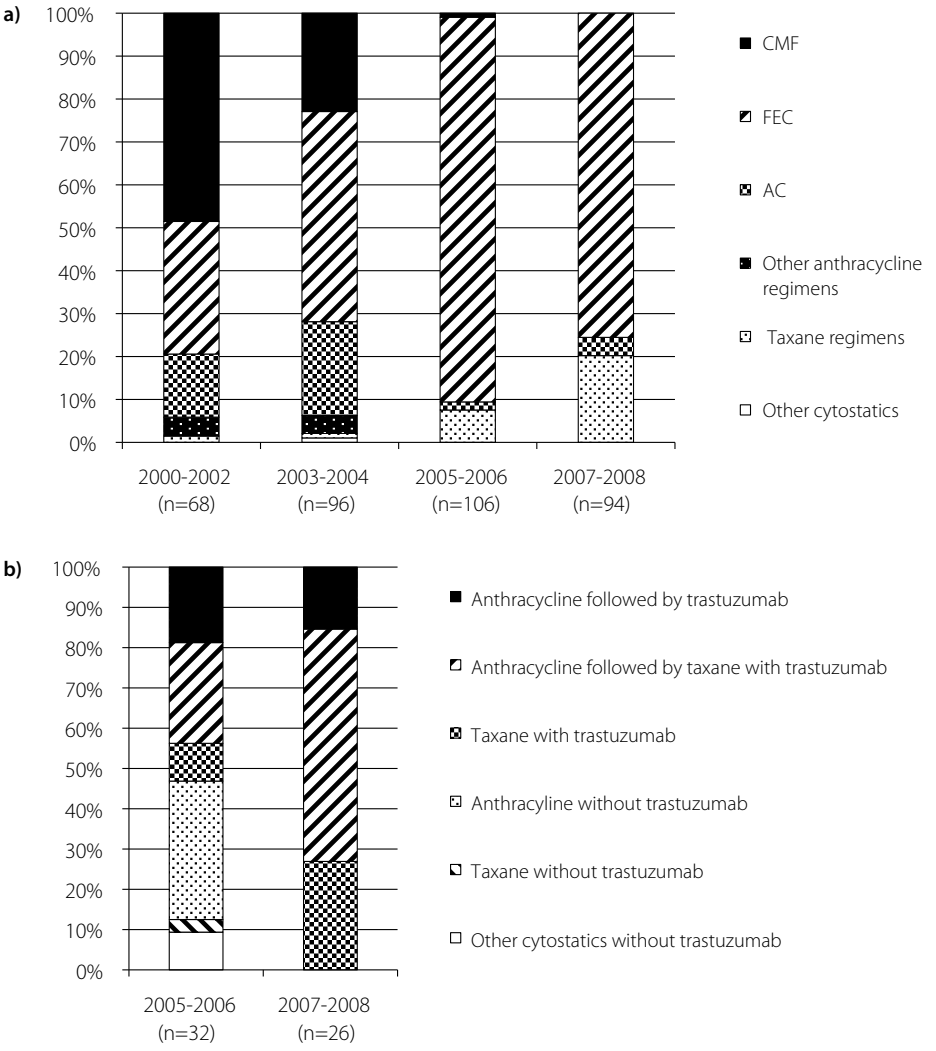

Figure 2. Proportion of patients receiving a specific type of adjuvant chemotherapy regimen over four periods of time by a) Her2/neu negative or unknown and b) Her2/neu positive.

CMF: cyclophosphamide, methotrexate, 5-fluorouracil; FEC: 5-fluorouracil, epirubicin, cyclophosphamide; AC: doxorubicin, cyclophosphamide. The distribution of adjuvant chemotherapy regimens administered to patients with Her2neu overexpression is presented from the period 2005-2006 onwards as Her2/neu status was registered from 2005 onwards.

For the adjuvant administered chemotherapies, the proportion of patients receiving a specific chemotherapy combination over time was stratified by Her2/neu status. For patients diagnosed with a Her2/neu negative tumour or unknown Her2/neu status (Figure

2a), the choice of CMF as adjuvant treatment decreased over time (from 49% in 2000-2002 to none in the period 2007-2008) and the use of FEC changed from 31% in 2000-2002 to 90% in 2005-2006 and 76% in 2007-2008. Almost half of the patients (47%) diagnosed with Her2/neu overexpression in the period 2005-2006, did not receive a chemotherapy regimen containing trastuzumab (Figure 2b). Of these, 80% were treated in 2005. In contrast, in the period 2007-2008 all patients diagnosed with Her2/neu overexpression received a trastuzumab containing regimen of which the majority (58%) received an anthracycline based regimen followed by a taxane with trastuzumab.

Discussion

The type of chemotherapeutics administered in daily practice to patients with early stage and metastatic breast cancer has changed markedly in the period 2000-2008. While patients in the adjuvant setting were in general treated according to the guidelines, there was a larger variation in the palliative setting.

In the year 2000 the majority of the early stage breast cancer patients received CMF (90%), while in 2005 almost all patients received anthracycline based regimens without taxanes (94%). These utilization patterns reflect the changes in the Dutch guidelines which were based on the studies presented in the meta-analyses of the Early Breast Cancer Trialists' Collaborative Group in 2005, concluding a superiority of anthracycline based regimens over CMF[18]. From 2005 onwards, the use of taxane based regimens (including regimens with anthracycline plus taxane) increased. This also reflects the revised guidelines which were based on the results of multiple trials supporting the use of taxane-containing regimens over non-taxane-containing regimens[19]. The presented increase of trastuzumab containing regimens among early stage breast cancer patients since 2005 is also in accordance with the Dutch guidelines. These were based on trials showing improved disease-free and overall survival among women with Her2/neu positive breast cancer after treatment with trastuzumab[20, 21]. For neoadjuvant chemotherapy, choice of type of treatment is based on the same criteria as for adjuvant therapy (Her2/neu status, nodal status, age and performance status)[22]. In our study, the distribution of the types of neoadjuvant chemotherapy administered was similar to the distribution of all the agents used in the adjuvant setting.

Although various population-based studies presented the overall pattern of chemotherapy among breast cancer patients over time[13-15, 23-26], only three also showed data on the specific types of chemotherapy[13-15], however, not beyond the year 2004. The trends in the use of CMF, anthracycline and taxane based regimens seen in these studies are continued in our study period. The study of Harlan *et al.*[13] and Giordano *et al.*[15] presented results from the SEER (Surveillance, Epidemiology and End Results) registry over the period 1987-1995 and 1991-1999, respectively. These studies already showed a decrease in the use of CMF and an increase of anthracycline-based chemotherapies (CAF and AC) and taxanes[13, 15].

A study of Shen *et al*.[14] at the M.D. Anderson Cancer Centre also showed that the use of anthracycline plus taxane chemotherapy already increased from 1997 onwards (17% in 1997 to 81% in 2004) and that the use of anthracyclines without taxanes had dropped among lymph node positive breast cancer patients (from 76% in 1997 to 20% in 2000)[14]. The more rapid changes seen in the study of Shen *et al*.[14] compared to our study might be due to the fact that 20% of the patients were treated within clinical trials, while in our study no data of academic hospitals are included.

From 2005 onwards, Her2/neu status had a major influence on the type of adjuvant chemotherapy prescribed and therefore information on Her2/neu overexpression has been recorded in the ECR from this year onwards. Of the patients diagnosed with Her2/neu overexpression who did not receive a cytostatic regimen containing trastuzumab in the adjuvant setting in the period 2005-2006, 80% were treated in 2005. These patients were probably already treated before the implementation of the new guidelines in september 2005, advising trastzumab to early stage breast cancer patients with Her2/neu overexpression[10]. All other Her2/neu positive patients diagnosed in 2006, 2007, 2008 were treated with trastuzumab, except for two patients diagnosed in 2006. Not all patients diagnosed with Her2/neu overexpression are acceptible candidates for trastuzumab because of the possible cardiotoxicity of trastuzumab.[27] Of the patients diagnosed with Her2/neu overexpression who were not yet treated with trastuzumab in the adjuvant setting and were diagnosed with recurrent breast cancer (N=21), the majority (86%) did receive trastuzumab in the palliative setting.

In our study we assumed that restart of chemotherapy after 90 days indicated a distant recurrence as secondary adjuvant chemotherapy for the treatment of a local recurrence is not recommended[22]. Results on the use of chemotherapy of patients with metastases at diagnosis or during follow-up were presented together, as these patients are expected to be treated in a similar way. Patients with a distant recurrence received slightly more often an anthracycline plus taxane instead of an anthracycline alone, probably because they already had received anthracyclines in the adjuvant setting. The lack of widely accepted patient-specific treatment guidelines for metastatic breast cancer is the result of the high variability in individual presentation. Therefore, clinicians must determine which therapeutic intervention is most appropriate for each patient, based on the patient and tumour characteristics, the number and sites of metastases, vital organ involvement, previous treatments and the previous disease-free survival interval.[4, 22] While it seems unlikely that any single agent or combination regimen will emerge as superior in the near future, progress in chemotherapeutic treatment of metastatic breast cancer is made[28] and our study did present trends in chemotherapy use. The use of CMF decreased from around 50% in the period 2000-2003 to no use in 2008 and new treatments that were approved for the treatment of metastatic breast cancer, such as bevacizumab, entered the palliative setting.

Data on specific type of single agent or multidrug chemotherapy were available for only 25% of the breast cancer patients included in the ECR-PHARMO cohort. With expansion of the in-hospital pharmacy database in the near future, studies on in-hospital variety

and presenting the various chemotherapy regimens by for example nodal status, age, performance status and socio-economic status will be possible. Next to treatment pattern studies also outcome studies will be possible, which is important as with a growing pool of active drugs for the treatment of breast cancer, their long-term toxicity profiles come into focus when considerations turn to cure and preservation of quality of life.
The results from our study suggest that key findings in chemotherapeutic treatment for breast cancer patients from large clinical trials over the last decade were incorporated in the Dutch guidelines, which resulted in substantial changes in patient care practices in community hospitals in the southeastern Netherlands.

Acknowledgement

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Half of breast cancer patients discontinue tamoxifen and any endocrine treatment before the end of the recommended treatment period of five years: a population-based analysis

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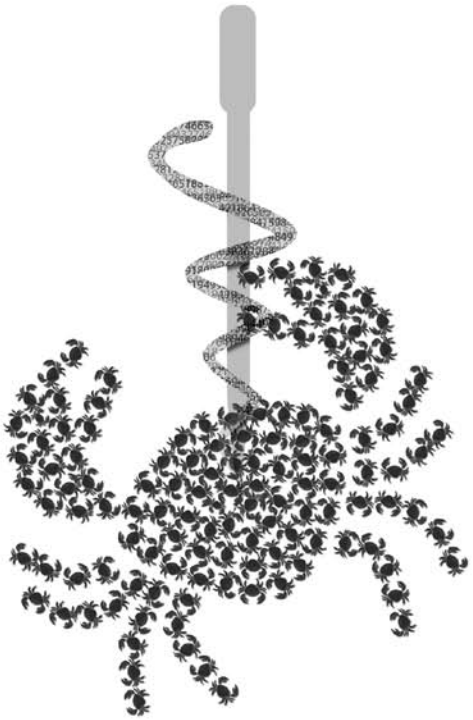


Abstract

Background:
Observational studies on long-term endocrine treatment among breast cancer patients have presented discontinuation rates on tamoxifen, but lack information on the continuance of any endocrine treatment (both tamoxifen and aromatase inhibitors (AI)) within the same cohort.

Objectives:
To determine switching rates from tamoxifen to AIs, discontinuation rates of tamoxifen only, discontinuation rates of any endocrine treatment and determinants of first treatment switch and treatment discontinuation.

Methods:
Patients with early stage breast cancer (stage I-IIIa) starting on tamoxifen were selected from the linked Eindhoven Cancer Registry-PHARMO RLS cohort in the period 1998 to 2006. Continuous use (allowing a 60 days gap between refills) of tamoxifen only and any endocrine treatment were determined after various follow-up periods: 1,2,3,4 and 5 years. Time to first switch from tamoxifen to an AI was assessed. Cox regression was used to identify determinants of first treatment switch, discontinuation of tamoxifen and discontinuation of any endocrine treatment.

Results:
A total of 1,451 new early stage breast cancer patients started on tamoxifen. Of those, 380 had a treatment switch to an AI during follow-up. Of the patients followed for five years, 40% continuously used tamoxifen, which was 49% for any endocrine treatment. Older age (older than 70 versus 50-69 years) was independently associated with increased discontinuation of tamoxifen and any endocrine therapy. Patients with two or more concomitant diseases (versus no co-morbidity) showed an increased likelihood to stop any endocrine treatment or switch treatment from tamoxifen to an AI.

Conclusions:
Up to half of the breast cancer patients starting tamoxifen continued five years of endocrine treatment. Identification of patients at risk of discontinuation will assist in the development of interventions to improve treatment continuation comparable to that of patients included in clinical trials.

Introduction

Adjuvant endocrine treatment in women with early stage breast cancer significantly prolongs disease free and overall survival time[1, 2]. For nearly 20 years the anti-oestrogen tamoxifen was the standard endocrine adjuvant treatment used for postmenopausal women with hormone receptor-positive early stage breast cancer[1]. In the late nineties of the previous century, aromatase inhibitors (AIs) became available for the treatment of postmenopausal women with hormone receptor-positive advanced breast cancer. Since about five years AIs also have been approved for the adjuvant treatment of women with hormone receptor positive, early stage breast cancer[2].

Discontinuation with endocrine therapy among early stage breast cancer patients in daily practice has become a widespread concern. While breast cancer patients are likely to be highly motivated to continue endocrine treatment[3], many studies using pharmacy, medical and health insurance records have reported high rates of discontinuation of tamoxifen ranging from 35% to 51% in study periods of 3.5 to 5 years[4-6].

The question remains whether these patients actually stop endocrine treatment or whether they switch from tamoxifen to an aromatase inhibitor. Recently, a study using health insurance records, reported rates of treatment discontinuation of all types of endocrine treatment together (tamoxifen, anastrozole, letrozole or exemestane): 20% of the women discontinued endocrine treatment after one year of follow-up[7]. Moreover, one recent chart review reported next to treatment discontinuation, results on switching from first-line endocrine therapy[8]. However, to our knowledge there are no published studies with five years of follow-up in which discontinuation rates on both tamoxifen only and any endocrine treatment have been studied.

Among early stage breast cancer patients we determined the following during the first five years after start of tamoxifen: switching rates from tamoxifen to AIs, discontinuation rates of tamoxifen only, discontinuation rates of any endocrine treatment and determinants of first treatment switch and treatment discontinuation. For a sub-cohort of patients, the date of first breast cancer recurrence was studied in relation to the date of discontinuation of tamoxifen or switch from tamoxifen to an AI.

Methods

Data Source

Data were obtained from the Eindhoven Cancer Registry (ECR) linked on a patient-level to the PHARMO Record Linkage System (PHARMO RLS) covering a demographic region in the southeastern part of the Netherlands of approximately one million inhabitants. The construct, validity and contents of the PHARMO-ECR cohort are described elsewhere.[9]

Study population

The source population included all women registered in the PHARMO-ECR cohort in the period 1998–2006 diagnosed with early stage breast cancer (stage I-IIIa). Of these, it was determined whether they started endocrine treatment (cohort entry date) in the first year after diagnosis. Patients were followed from the cohort entry date onwards and were censored at time of hospitalisation for cancer other than breast cancer (ICD-9-CM codes 140-230 excl. 174, 196, 197, 198 or 199), death, loss to follow-up in the PHARMO RLS, or end of study period (December 31, 2007), whichever occurred first.

Endocrine treatment of early stage breast cancer

In our study period, five years of tamoxifen only, five years of AIs (anastrozole, letrozole and exemestane) or sequential therapy of 2-3 years of tamoxifen followed by 3-2 years of AIs were advised in the Dutch guidelines. Treatment choice was dependent on the patient characteristics such as menopausal status and tumour characteristics such as Her2/neu status. Patients intolerant of one type of endocrine therapy were advised five years of treatment with the other.[10, 11] As starting on AI was advised in the guidelines from 2004 onwards, patients starting on AI were excluded from further analyses as they did not have five years of follow-up time.

Treatment discontinuation and switching

Treatment continuation is defined as the percentage of patients who used the drug during a specific period of time without failure to continue renewals.[12, 13] In this study, treatment continuation was assessed using episodes of endocrine treatment based on the method published by Catalan and LeLorier.[14] To assemble endocrine treatment episodes, the duration of use of each dispensing was calculated by dividing the number of units dispensed by the number of units to be used per day, as defined in the pharmacies. In case of an interruption between two dispensings, the episode was considered uninterrupted if the duration of this gap was less than the permissible gap of 60 days[6]. We additionally performed sensitivity analyses allowing a gap of 90 days[7] and 180 days[4, 5]. The treatment episode was measured as the time span between the start of the first dispensing until the end of the final dispensing. The latter was set at half the duration of time after the last date that the drug was dispensed, with the assumption that patients stopped their medication somewhere in time after filling their last prescription. Treatment continuation with tamoxifen was defined as the number of days from start of therapy (cohort entry date) to the date of first failure to continue renewals of tamoxifen (end date of the first treatment episode) or the start date of an AI (switch), whichever occurred first. In addition, we assessed treatment continuation with any endocrine therapy (irrespective of type of treatment; tamoxifen or AIs), i.e. the number of days of continuous use of any endocrine therapy from cohort entry date onwards. Treatment episodes of continuous use of tamoxifen (initial treatment) and any endocrine therapy were defined up to 5 years, following the guidelines.[10, 11]

Determinants of treatment discontinuation

The following potential determinants of discontinuation of tamoxifen, first treatment switch and discontinuation of any endocrine treatment were considered, based on available information in the PHARMO-ECR cohort, clinical knowledge and recently published studies[4, 6, 15-17]: age, hormone receptor status, tumour size, lymph node status, histologic tumour grade, treatments other than endocrine treatment (surgery, chemotherapy and radiation therapy), co-morbidity at diagnosis according to a slightly modified version of the Charlson classification[18], drug treatment in the year before cohort entry, the number of different drug classes used (anatomical classes ATC level 1, excluding use of endocrine treatment) and socio-economic status.

Breast cancer recurrence

Since 1989, the Eindhoven Cancer Registry has recorded follow-up information for a sub-cohort of breast cancer patients diagnosed in the eastern part of the region. Follow-up information included the date and site of local, regional and distant recurrence. In contrast to the actively performed data collection on diagnosis and treatment of the primary tumour, this follow-up information is a passive registration. Histologic or cytologic confirmed breast cancer recurrences are provided by the pathology departments and assumed to be complete. However, information on breast cancer recurrences without a cytologic or histologic confirmation had to be provided by surgeons, radiotherapists and oncologist and was not actively collected. This means that there was an unknown amount of underreporting. No breast cancer recurrence can mean that a woman was indeed disease free or that the data is missing. For the patients included in our study population, date of the first reported breast cancer recurrence was defined when recorded before loss to follow-up in the PHARMO RLS, or end of study period (December 31, 2007).

Analyses

Baseline and treatment characteristics of early stage breast cancer patients who did not switch (tamoxifen use only) and patients who switched to an AI were compared using the Chi-square test. Survival functions describing the proportion of continuous drug users over time for a) tamoxifen use only or b) any endocrine treatment, were computed using Kaplan-Meier survival analyses with treatment discontinuation or –in case of tamoxifen use only- switch to an AI, considered as elimination and censoring patients who were considered lost to follow-up. Rates of endocrine treatment discontinuation were determined at 1,2,3,4 and 5 years after start tamoxifen treatment. Cox proportional hazards regression models were used to identify independent determinants of discontinuation of tamoxifen, switch to an AI or discontinuation of any endocrine treatment within five years after start of treatment (cohort entry date). Adjusted hazard ratios (HR) and 95% confidence intervals (CI) are presented for independent variables, with variables associated with treatment change (discontinuance or switch) in the univariate analyses included in the multivariate analyses. Statistical significance was defined at an alpha level of 0.05. For

a sub-cohort of patients with data on breast cancer recurrence, the date of first breast cancer recurrence was set out against the date of first treatment change: either stop with endocrine (tamoxifen) treatment or switch to an AI and the linear correlation between these dates was determined using the Pearson correlation test. Data were analysed using SAS programs that are organised within SAS Enterprise Guide version 4.1 (SAS Institute Inc., Cary, NC, USA). Data management was conducted under UNIX using SAS version 9.1.

Results

The PHARMO-ECR cohort included 4,917 women diagnosed with early stage breast cancer in the period 1998-2006 of whom 1,725 (35%) started endocrine treatment in the first year after diagnosis (Figure 1). The median duration (interquartile range) between diagnosis and start of endocrine treatment was 2 (1-5) months. Of the 1,725 patients, 1,451 (84%) started on tamoxifen and 274 (16%) started treatment with an AI. There were no patients who started on the anti-oestrogen fulvestrant or the AI aminoglutethimide in the first year after diagnosis. The 1,451 patients starting on tamoxifen were included in the study cohort. They had a mean follow-up of 4.1±2.4 years in the PHARMO RLS. Patients were censored at time of hospitalisation for cancer other than breast cancer (7%), death (15%), loss to follow-up in the PHARMO RLS (17%), or end of study period at December 31, 2007 (61%).

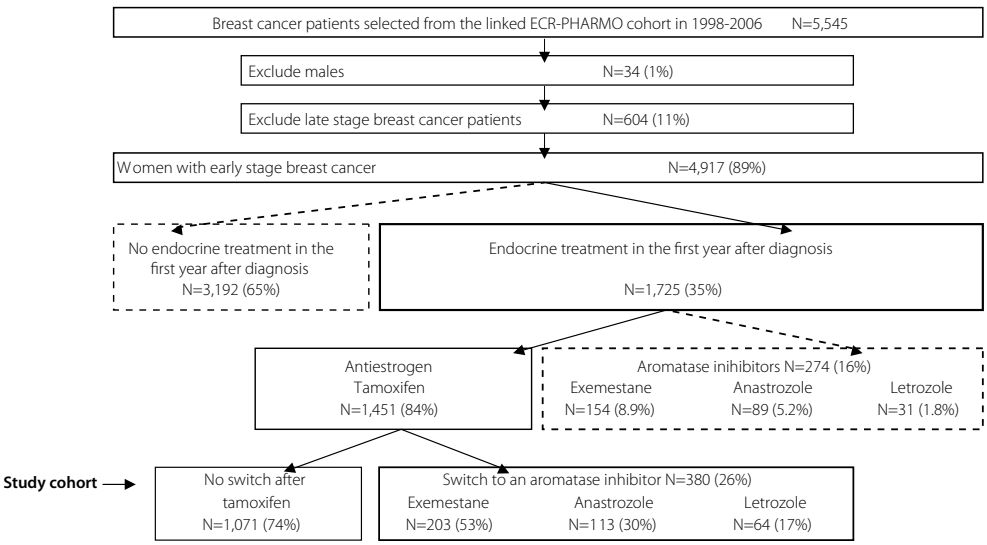


Figure 1. Flowchart patient selection.

Of the patients who started on tamoxifen, 380 (26%) switched to an AI during follow-up (Table 1). Patients who switched to an AI were younger than patients who used tamoxifen only; mean age (±SD) of 57 (±12) years versus 62 (±15) years (p<.0001). They started treatment in the more recent years, had received more often surgery, chemotherapy and radiotherapy, had used more different classes of drugs in the year after starting on tamoxifen and had a higher socio-economic status. When not taking into account the proportion of patients with an unknown lymph node status, there was no difference in lymph node status between patients who only used tamoxifen and patients who switched to an AI.

Table 1. Characteristics at diagnosis of early stage breast cancer patients, by type of endocrine treatment

Characteristics at diagnosis	Tamoxifen only and no switch (N=1,071) %	Tamoxifen and switch to Aromatase inhibitor (N=380) %	*p*-value
Age			<.0001
≤ 35 years	2	2	
36-49 years	21	26	
50-59 years	21	31	
60-69 years	21	23	
≥ 70 years	35	18	
Period of diagnosis			<.0001
1998-2001	46	26	
2002-2003	20	39	
2004-2006	34	35	
Hormone receptor status			0.187
ER+ and/or PR+	76	81	
ER- and PR-	2	1	
Unknown	22	18	
Tumour size			0.503
≤1.0 cm	9	7	
1.1-2.0 cm	39	40	
2.1-5.0 cm	46	47	
> 5.0 cm	5	6	
Lymph node status			0.001
Positive	29	27	
Negative	66	72	
Unknown	6	1	

Characteristics at diagnosis	Tamoxifen only and no switch (N=1,071) %	Tamoxifen and switch to Aromatase inhibitor (N=380) %	*p*-value
Histologic tumour grade			0.133
Well	15	15	
Moderate	32	32	
Poor	21	26	
Unknown	32	27	
Therapies other than endocrine			
Surgery (yes)	96	99	0.004
Chemotherapy (yes)	31	46	<.0001
Radiotherapy (yes)	65	74	0.002
Number of co-morbidities at diagnosis			0.522
None	82	82	
1	4	4	
≥ 2	4	3	
Unknown	10	11	
Most frequent co-morbidities at diagnosis			
Lung disease	4	5	0.670
Cardiovascular disease (incl. hypertension)	26	20	0.094
Diabetes	8	6	0.372
Number of different drug classes used in the year after start tamoxifen			<.0001
0-1 class	8	1	
2-3 classes	12	15	
4-5 classes	24	32	
≥ 6 classes	24	26	
Unknown[1]	31	27	
Socio-economic status			0.030
High	28	34	
Intermediate	39	39	
Low	26	23	
Institutionalized (nursing homes)	6	2	
Unknown	1	1	

ER: Oestrogen receptor; PR: Progesterone receptor; [1] Not able to define number of drug classes used in the year after cohort entry as patients were not registered for 1 year or more in the PHARMO RLS after cohort entry.

The percentage of continuous users of tamoxifen only (N=1,071) at 1, 2, 3, 4 and 5 years was 83%, 70%, 55%, 50% and 40%, respectively (Figure 2a). Sensitivity analyses showed that allowing a gap of 90 or 180 days instead of 60 days increased the percentage of continuous users of tamoxifen at 5 years; 50% and 56%, respectively. Of the 380 patients who switched to an AI, the largest decrease in continuance of tamoxifen (switch to an AI) was shown in the period from 2 to 3 years: from 55% to 25%. The mean duration (± SD) of tamoxifen use until switch was 1.9 ± 1.2 years until switch to anastrozole, 2.0 ± 1.3 years until switch to exemestane and 2.1 ± 1.4 years until switch to letrozole.

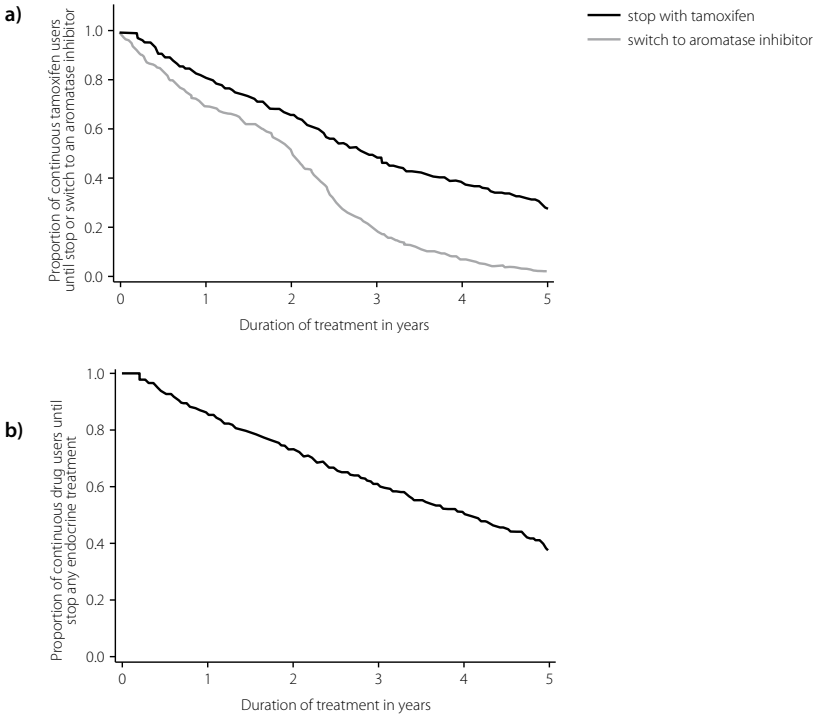


Figure 2 a-b. Proportion of early stage breast cancer patients who start tamoxifen therapy: a) continue tamoxifen over a 5-year follow-up period until first treatment change: stop with tamoxifen treatment (N=1,071) or switch to an aromatase inhibitor (N=380) b) continue any endocrine treatment (irrespective of type of endocrine treatment) over a 5-year follow-up period (N=1,451).

The percentage of continuous users of any endocrine treatment at 1, 2, 3, 4 and 5 years was 87%, 78%, 69%, 63% and 49%, respectively (Figure 2b). Allowing a gap of 90 or 180 days instead of 60 days showed an increase of the percentage of continuous users of any endocrine treatment at 5 years; 59% and 66%, respectively.

Table 2. Determinants of discontinuation of tamoxifen due to stop of endocrine treatment or switch to an aromatase inhibitor and stop with any endocrine therapy within five years after start

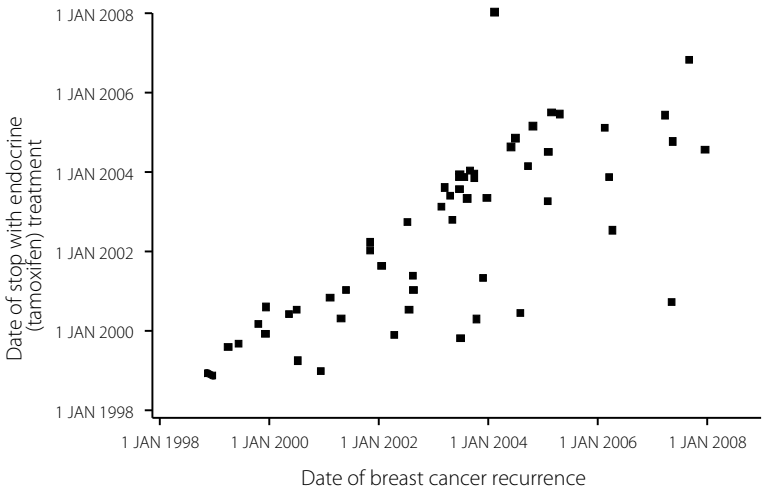
	Early stage breast cancer patients who start tamoxifen therapy					
	Stop with tamoxifen treatment (N=1,071)		Switch to an aromatase inhibitor (N=380)		Total, stop with any endocrine treatment (N=1,451)	
Characteristics	**HR Adjusted[1]**	**95% CI**	**HR Adjusted[1]**	**95% CI**	**HR Adjusted[1]**	**95% CI**
Age at diagnosis						
≤ 49 years	0.83	(0.65-1.05)	0.77	(0.46-1.30)	0.77	(0.60-1.01)
50-69 years	0.74	(0.61-0.90)	0.83	(0.53-1.28)	0.71	(0.59-0.85)
≥ 70 years	1	-	1	-	1	-
Tumour size						
≤1.0 cm	1	-			1	-
1.1-2.0 cm	0.98	(0.72-1.34)			0.96	(0.72-1.27)
2.1-5.0 cm	1.12	(0.82-1.53)			1.05	(0.79-1.39)
> 5.0 cm	1.45	(0.93-2.26)			1.28	(0.86-1.91)
Number of co-morbidities at diagnosis						
None	1	-	1	-	1	-
1	0.87	(0.55-1.39)	2.08	(1.01-4.31)	1.03	(0.70-1.53)
≥ 2	1.30	(0.88-1.92)	4.56	(1.96-10.6)	1.58	(1.10-2.25)
Unknown	0.83	(0.61-1.12)	1.44	(0.88-2.35)	0.93	(0.72-1.20)
Number of different drug classes used in the year after start tamoxifen						
0-1 class	1	-	1	-	1	-
2-3 classes	0.82	(0.62-1.07)	1.04	(0.58-1.85)	0.82	(0.64-1.05)
4-5 classes	0.89	(0.68-1.17)	1.42	(0.79-2.53)	0.96	(0.75-1.23)
≥ 6 classes	1.15	(0.89-1.49)	1.68	(0.95-2.98)	1.21	(0.96-1.54)
Socio-economic status						
High					1	-
Intermediate					1.00	(0.83-1.21)
Low					1.11	(0.91-1.37)
Institutionalized or unknown					1.08	(0.76-1.54)

HR: hazard ratio; [1]Adjusted for variables potentially associated with discontinuance in the crude analyses ($p < 0.05$).

Multivariate analyses in Table 2 show that patients who did not continue tamoxifen were less likely to be aged 50-69 years (versus ≥70 years; hazard ratio (HR)=0.74; 95%CI: 0.61-0.90). This was also seen for discontinuation of any endocrine therapy (50-69 years versus ≥70 years; HR=0.71; 95%CI: 0.59-0.85). Moreover, multivariate analyses showed that patients who did not continue any endocrine therapy were more likely to have 2 or more concomitant diseases (versus no co-morbidity; HR=1.58; 95%CI: 1.10-2.25). Multivariate analyses of switch from tamoxifen to an AI showed that women with one or multiple co-morbidities were more likely to switch from tamoxifen to an AI than patients without co-morbidities at diagnosis: HR=2.08 (95%CI: 1.01-4.31) for patients with one co-morbidity and HR=4.56 (95%CI: 1.96-10.6) for patients with two or more co-morbidities.

Of the 1,451 patients starting on tamoxifen, 98 patients were known to have developed a breast cancer recurrence during follow-up. For these patients, the date of first treatment change (either stop or switch) was set out against the date of first breast cancer recurrence (Figure 3a and 3b). The average time (± SD) from cohort entry until first breast cancer recurrence was 2.8 (±1.8) years. Of the 56 women with a breast cancer recurrence who stopped with endocrine treatment (N=21 with a local/regional recurrence and N=35 with a distant recurrence), the date of stop and date of recurrence were significantly correlated (r=0.74, p<.0001). Of the 42 women with a breast cancer recurrence who switched from tamoxifen to an AI during follow-up (N=12 with a local/regional recurrence and N=30 with a distant recurrence), the date of switch and date of recurrence were even more significantly correlated (r=0.93, p<.0001).

a)



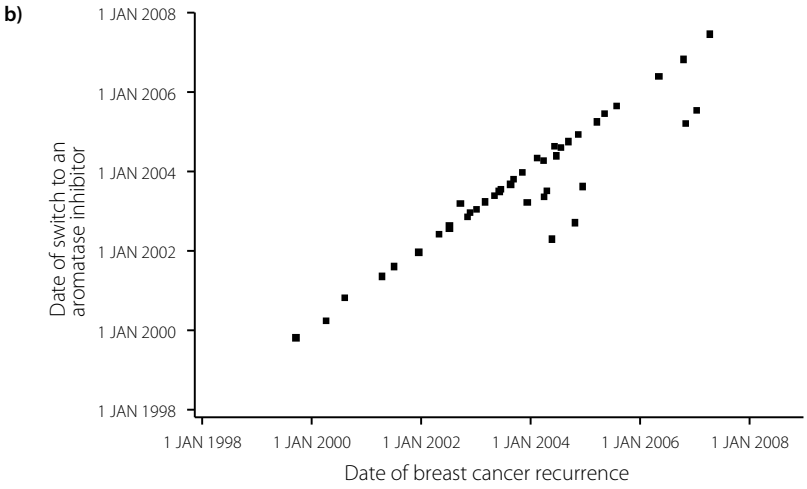


Figure 3 a-b. Of the patients of whom a breast cancer recurrence was reported during follow-up (N=98) the date of first treatment change was set out against the date of first breast cancer recurrence. With treatment change defined as a) stop with endocrine (tamoxifen) treatment (N=56) or b) switch to an aromatase inhibitor (N=42).

Discussion

This observational study showed that in daily practice 40% to 56% of patients with early stage breast cancer continuously used tamoxifen over a five year follow-up period, allowing a permissible gap of 60 to 180 days, respectively. When evaluating the use of all types of endocrine treatment together (tamoxifen, anastrozole, letrozole or exemestane) and allowing patients to switch endocrine treatment multiple times, the percentage of patients continuously using any endocrine treatment over a five year follow-up period was still only 49% to 66%. Increasing the permissible gap from 60 to 180 days indicates that around 15% of the patients restart treatment during five years of follow-up.

To date, multiple clinical trials have demonstrated that five year use of adjuvant endocrine treatment among patients with hormone receptor positive, early stage breast cancer improves disease-free and overall survival[1, 19, 20]. However, high discontinuation rates as reported in this observational study, lower the benefit found in clinical trials. These high discontinuation rates were also found in previous studies on tamoxifen use using pharmacy, medical and insurance records,[4-6] especially when the same permissible gap and study follow-up period were taken into account.

In this study, older age (older than 70 versus 50-69 years) was independently associated with increased discontinuation of tamoxifen. Other studies also found that extremes of age (under 45 and over 75) were associated with tamoxifen discontinuation and non-

adherence.[4, 6, 15-17] For any endocrine therapy, having two or more concomitant diseases versus no co-morbidity was, next to older age, also associated with an increased likelihood to discontinue any endocrine therapy. Owusu *et al.*[6] found that an increase in Charlson co-morbidity index at 3 years from diagnosis was related with an increased likelihood to discontinue tamoxifen treatment, suggesting that patients discontinue treatment due to other life threatening diseases.

Previous studies using self-report questionnaires or telephone interviews on non-adherence or discontinuation of tamoxifen have reported that reasons for discontinuation vary, ranging from treatment related side effects, simply forgetting to take the medication, to lack of confidence in prescribed endocrine treatment.[3, 15, 16, 21-25] Psychological factors, particularly depression and anxiety also seem to contribute to treatment discontinuation. However, in our study we did not find an increased likelihood to discontinue endocrine treatment among women who received antidepressants in the year before tamoxifen initiation (10% of the women included in the study cohort).

The observational study of McCowan *et al.*[5] showed that decreased duration of tamoxifen use in daily practice increased the risk of all cause mortality. However, the influence of breast cancer recurrence on the decision to stop with tamoxifen could not be established, as the authors commented this to be difficult to ascertain within a community setting.[5] In our study data on breast cancer recurrence were only available for a sub-cohort, due to the fact that no active follow-up had taken place of the patients documented by the Eindhoven Cancer Registry. Nevertheless, presenting the date of first breast cancer recurrence and date of stop with tamoxifen treatment showed that most patients with a breast cancer recurrence stopped tamoxifen treatment. Future observational database studies should report whether they have information on breast cancer recurrence and/or exclude these patients from further analyses, as has been done in previous interview and questionnaire studies[21, 23].

Of the patients who switched treatment from tamoxifen to an AI, most switched after 2 to 3 years of tamoxifen use. This is in accordance with the guidelines advising switching of treatment in this period and this is also reported in a recent performed retrospective chart review[8]. Switching to an AI within 2 years after starting on tamoxifen could be due to intolerability to tamoxifen and switching within 2 years or after 3 years of tamoxifen treatment could be due to, among other things, a breast cancer recurrence. In our study, patients having one or more concomitant diseases versus no co-morbidity were more likely to switch from tamoxifen to an AI. Moreover, we found a strong correlation between date of breast cancer recurrence and date of switch. Schwartzberg and colleagues[8] performed exploratory telephone interviews to determine reasons for switching and nearly all patients cited doctor recommendation or side effects as a reason for switching.

In this study we were only able to report discontinuation rates of patients starting on tamoxifen as at the moment of the study, patients starting on AIs had too short follow-up time to be able to report five year discontinuation rates. While several studies have reported treatment discontinuation rates of patients starting with AIs after one year of

follow-up[7, 26, 27], long-term observational studies are needed in the future to determine treatment continuation and switching patterns during five years of follow-up of patients starting on AIs.

This study reports results of observational data, however, some of the patients included in our study cohort might be included in a post-marketing multinational trial[28]. As a result, continuous use of endocrine treatment among these patients might be increased compared to the rates found in daily practice. However, in this study we still found high overall discontinuation rates of endocrine treatment.

From the results of this study we conclude that up to half of the women to whom adjuvant tamoxifen treatment was prescribed stop taking tamoxifen before the end of the recommended treatment period of five years. Even after increasing the permissible gap and allowing multiple switching to other endocrine therapies, the rate of patients who discontinue endocrine treatment remained high. These high discontinuation rates lower the benefit of adjuvant endocrine treatment among women with hormone receptor positive, early stage breast cancer on disease-free and overall survival found in clinical trials. Identification of patients at risk of discontinuation of endocrine treatment, either or not intentionally, may help to improve treatment continuation.

Acknowledgements

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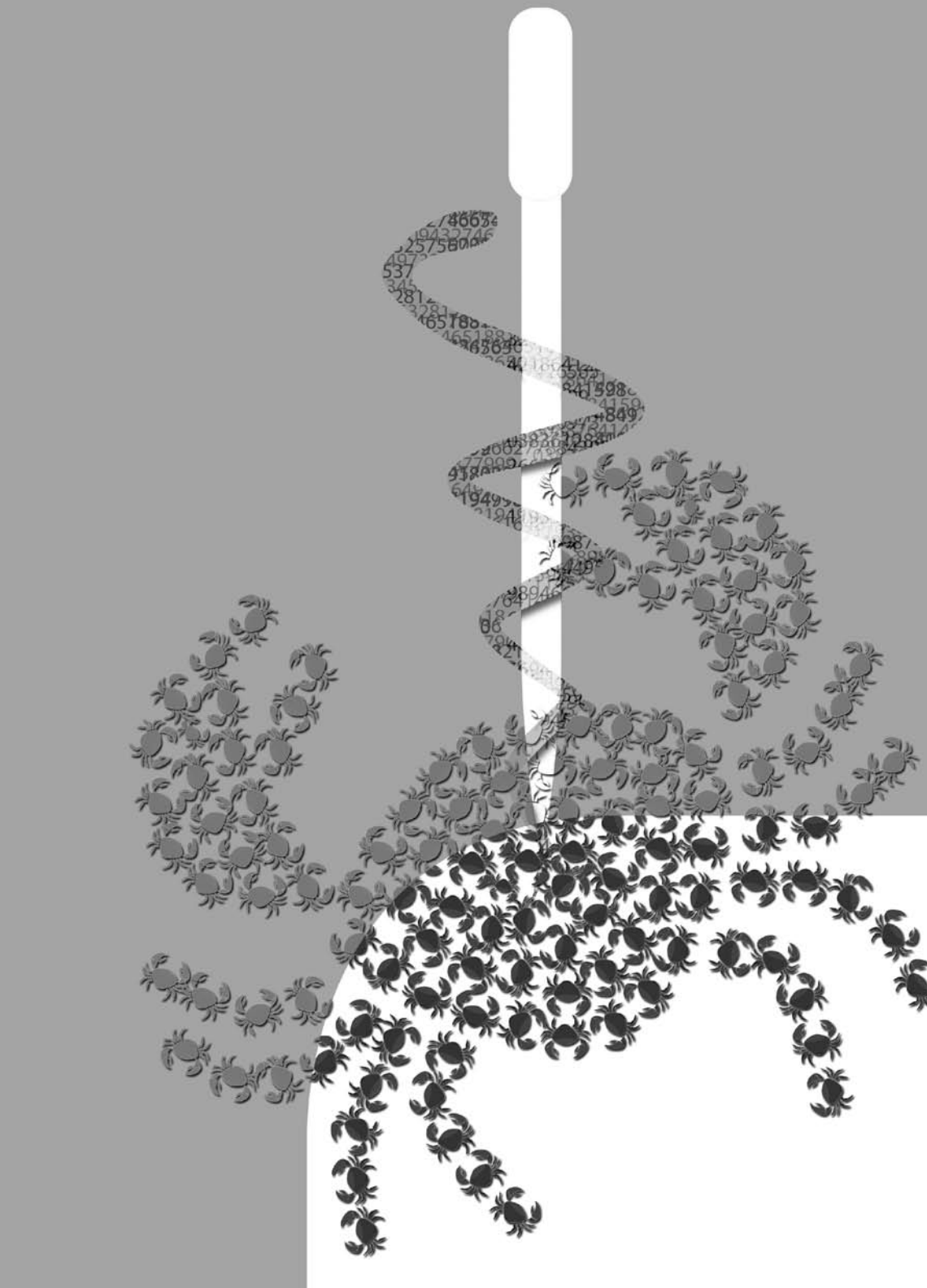
PART III NEW MORBIDITIES AFTER BREAST CANCER DIAGNOSIS AND TREATMENT



Incidence of cardiovascular events in breast cancer patients receiving chemotherapy in clinical practice

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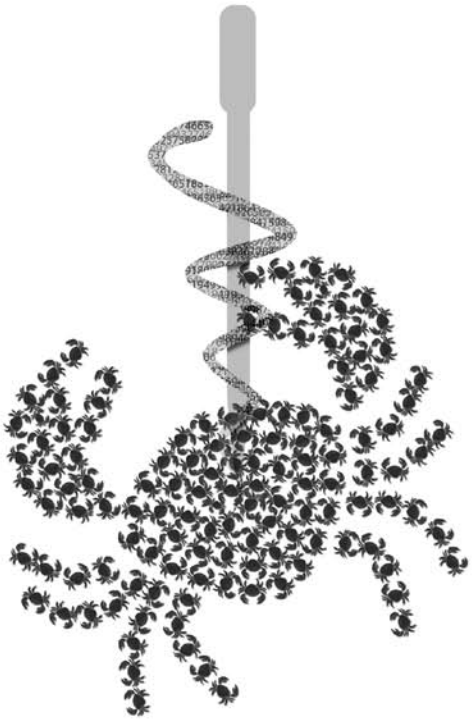

Abstract

Background:
Cardiotoxicity is a well-known side effect of several chemotherapeutics and may be the dose-limiting factor in chemotherapy.

Objectives:
To assess the incidence of cardiovascular events among breast cancer patients after chemotherapy.

Methods:
Women ≥ 18 years with a breast tumour who received chemotherapy in 1992-2003 were selected from the PHARMO RLS. Chemotherapy with anthracyclines, a combination of anthracyclines and taxanes, or second line treatment with trastuzumab was classified as cardiotoxic. Cardiovascular events were determined based on drug use and hospital admissions. Incidence rates of cardiovascular events and hazard ratios (HR) for the cardiotoxic versus non-cardiotoxic chemotherapy group were assessed during the first year and total follow-up.

Results:
Of 648 patients with breast cancer included in the study cohort, 353 (54%) received cardiotoxic chemotherapy. At baseline, patients who received cardiotoxic chemotherapy compared with patients receiving non-cardiotoxic chemotherapy, received less anticoagulants/haemostatics (5% versus 11%; p = 0.012) and had been less often hospitalized for cardiovascular disease (1% versus 5%; p = 0.007) two years before the cohort entry date.
After one year follow-up, the incidence rate of cardiovascular events was 69/1,000 py for patients with cardiotoxic chemotherapy and 98/1,000 person years (py) for patients with non-cardiotoxic chemotherapy, which did not differ significantly (HR 0.74 95%CI: 0.39, 1.41). After total follow-up, this was 81/1,000 py for patients with cardiotoxic and 92/1,000 py for patients with non-cardiotoxic chemotherapy (HR 0.81, 95%CI: 0.54, 1.20).

Conclusions:
This study showed similar cardiovascular incidence rates during follow-up for breast cancer patients treated with cardiotoxic and non-cardiotoxic chemotherapy. Specialists seemed to take pre-existing cardiovascular diseases into account when treating the breast cancer patient.

Introduction

Breast cancer is the most common cancer in women and every year over 300,000 women in Europe are diagnosed with the disease.[1] The type of treatment such as endocrine therapy, radiation therapy or chemotherapy, depends on the individual patient and tumour characteristics. Therefore, balancing effectiveness and adverse effect is a major challenge in the treatment of breast cancer patients.[2] Cardiotoxicity is a well-known adverse effect of several cytotoxic chemotherapy agents, notably the anthracyclines but also newer drugs such as trastuzumab in second line treatment.[3-9] It includes a wide range of cardiac effects from small changes in blood pressure and arrhythmias to serious cardiomyopathy and may lead to long term cardiovascular morbidity.[4-6, 8]

Incidences of cardiovascular events found in earlier studies are in the range of 0.5% to 20% depending on, among other things, dose of cardiotoxic drug, rate of administration of the cytotoxic chemotherapy agent and definition of cardiovascular event.[4, 6, 7, 9-11] Interactions between drugs such as taxanes and anthracyclines are likely to increase cardiotoxicity.[3] Other risk factors associated with cardiotoxicity include baseline characteristics such as age and a history of pre-existing cardiovascular disorders.[4, 6]

With the ageing of the population and the increasing survival of breast cancer patients with co-morbid conditions, cardiotoxicity of chemotherapy becomes increasingly important. Limited information is available on the background rates of cardiovascular disorders before and after chemotherapy among breast cancer patients in current clinical practice. The objective of the present study was therefore, to investigate the incidence of cardiovascular events in patients treated with chemotherapy in daily clinical practice and place this in the perspective of pre-existing cardiovascular risk factors and the specific chemotherapeutic agent used.

6

Methods

Data sources

This study was conducted with data from the PHARMO Record Linkage System (PHARMO RLS) which includes data from community and hospital pharmacies and hospital discharge records for more than two million individuals in defined areas in the Netherlands. Data from community pharmacies include information on the dispensed drug, the type of prescriber, the dispensing date, the amount dispensed, the prescribed dose regimens, and the legend duration of use (prescription length). All drugs are coded according to the Anatomical Therapeutic Chemical (ATC) Classification. The hospital discharge records include detailed information on admissions for more than 24 hrs and admissions for less than 24 hours for which a bed is required, concerning the primary and secondary diagnoses, procedures, and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM).

Data from hospital pharmacies contain per patient, complete information of in-hospital drug use, related to diagnoses and procedures. Because not all hospitals that participated in this study had electronically data available on chemotherapies, additional electronic and non-electronic data were obtained from the hospitals and added to the in-hospital pharmacy database.
Data on staging of cancer was obtained from the in-hospital files and the Eindhoven Cancer Registry (ECR). This registry records data of all malignant neoplasms in an area of 2.3 million inhabitants in the south of the Netherlands. Information is available on date of incidence, histology, topography, invasiveness, grade, stage and basis of diagnosis.

Study population

From the PHARMO RLS, incident patients with breast cancer were identified and defined as women aged 18 years or older who had been hospitalized for breast cancer (ICD-9-CM coding 174 and 198.81) from January 1992-December 2003. Patients were included if they had been treated with chemotherapy (ATC code: L01) in the period of less than two months before diagnosis or within six months after diagnosis. This period around the date of diagnosis was chosen because of the observed lag time between diagnosis and actual registration in the hospital files and the observed lag time between diagnosis and start of treatment after diagnosis. The date of the first chemotherapy during this period was defined as the cohort entry date. To ensure a reasonable time period to assess the patients' baseline status, we included patients only if they had a history of registration in PHARMO RLS for at least two years prior to the cohort entry date. Patients were followed from baseline until end of registration in PHARMO RLS (death or loss to follow-up), or end of study period (31 December 2003), whichever came first.
Of the patients included, age, year of start of chemotherapy and breast tumour stage at diagnosis, were determined at cohort entry date. Breast tumour staging was defined as specified by the American Joint Committee on Cancer (AJCC) TNM Classification of Malignant Tumours.[12, 13]

Breast cancer therapy

At cohort entry date, chemotherapy was classified in cardiotoxic treatment that included treatment with anthracyclines, a combination of anthracyclines and taxanes, or second line treatment with trastuzumab, and non-cardiotoxic treatment that included all other chemotherapies.[3-9]
Assessment of breast cancer therapy in the period of two years before the cohort entry date included breast surgery (yes/no), hormonal therapy (yes/no), chemotherapy (yes/no), and radiation therapy (yes/no). Data on radiation therapy were only available for the sub sample of patients registered in the ECR. Moreover, hospital admissions for breast cancer or other types of cancer were determined in the period of two years before the cohort entry date.
In addition, type of chemotherapy at baseline and during follow-up was classified based

on the most frequently used combinations. Chemotherapy was stratified in first, second and third line therapy, with switch from first to second line or second to third line therapy based on the start of a different type of chemotherapy agent, or a different combination of chemotherapy.

Cardiovascular co-morbidity

Cardiovascular co-morbidity was assessed based on drug use and hospital admissions as indicator for cardiovascular problems, in the period of two years before cohort entry date. This included use of anti-hypertensive drugs (ATC code: C02-C09), anti-diabetics (ATC code: A10), nitrates (ATC code: C01DA), anti-arrhythmics (ATC code C01B), digitalis (ATC code: C01AA05), anticoagulants/haemostatics (ATC code: B01) and lipid lowering drugs (ATC code: C10AA). Hospital admissions for cardiovascular disease (ICD-9-CM codes: 390-459; with valve disease: 394-397, 424; hypertensive disease: 401-405; myocardial infarction: 410, 412, 429.7; angina pectoris: 413; cardiomyopathy: 425; cardiac disturbances: 426-427; heart failure: 428; cerebrovascular disease: 430-438 and disease of arteries: 440-448) and diabetes (ICD-9-CM code: 250) were also determined. In addition, the potential impact of cardiovascular co-morbid conditions was classified into none/light impact, moderate impact or high impact by using a slightly adapted version of the conceptual model "Life Threat" by Yancik et al.[14]

Cardiovascular events

To identify incident cardiovascular adverse events, hospital admissions for cardiovascular diseases and cardiovascular drug use during the first year of follow-up and the total follow-up period were evaluated. Hospital admissions were always defined as an incident adverse event. Drugs were considered new and contributed to incidence rates if they had not been dispensed to the patient in the two years before the cohort entry date.

The incidence rate for a specific adverse event was calculated by dividing the number of patients with that specific incident adverse event by the sum of days of follow-up of all patients. Patients were followed from cohort entry date until that specific incidence adverse event, end of registration in PHARMO RLS (death or loss to follow-up), or end of study period (31 December 2003), whichever came first.

Statistical analysis

Baseline characteristics of patients treated with cardiotoxic chemotherapy were compared with patients treated with non-cardiotoxic chemotherapy using Student's t test (continuous variables) Chi-square (non-dichotomous categorical variables) or Fischer Exact (dichotomous variables). The incidence rates of cardiovascular adverse events were calculated, stratified for patients receiving cardiotoxic and non-cardiotoxic chemotherapy and assessed during the first year of follow-up and during total follow-up (long term adverse events). The incidence rates of cardiovascular adverse events were expressed in 95% confidence intervals based on Byar's approximation.[15] Hazard ratios, including

95% confidence intervals, for cardiovascular adverse events in the cardiotoxic treatment group, compared with the non-cardiotoxic treatment group, were calculated using the Cox proportional hazards regression analysis. Hazard ratios were also shown adjusted for age, year of cohort entry date and stage of cancer. All analyses were performed using SAS V9.1 UNIX (Cary, NC, USA).

Results

In total, 4,856 patients with a hospital admission for breast cancer were identified of whom complete data were available in the period 1992 to 2003. About 20% ($n = 953$) of these patients received chemotherapy and finally 648 patients were included in the study cohort based on available breast tumour staging data and the inclusion criteria. A flowchart of the patient selection for the study cohort is shown in Figure 1. The median follow-up of the patients included in the study cohort was 545 days (interquartile range: 240-1,045 days) and more than half of these patients received cardiotoxic chemotherapy (54%).

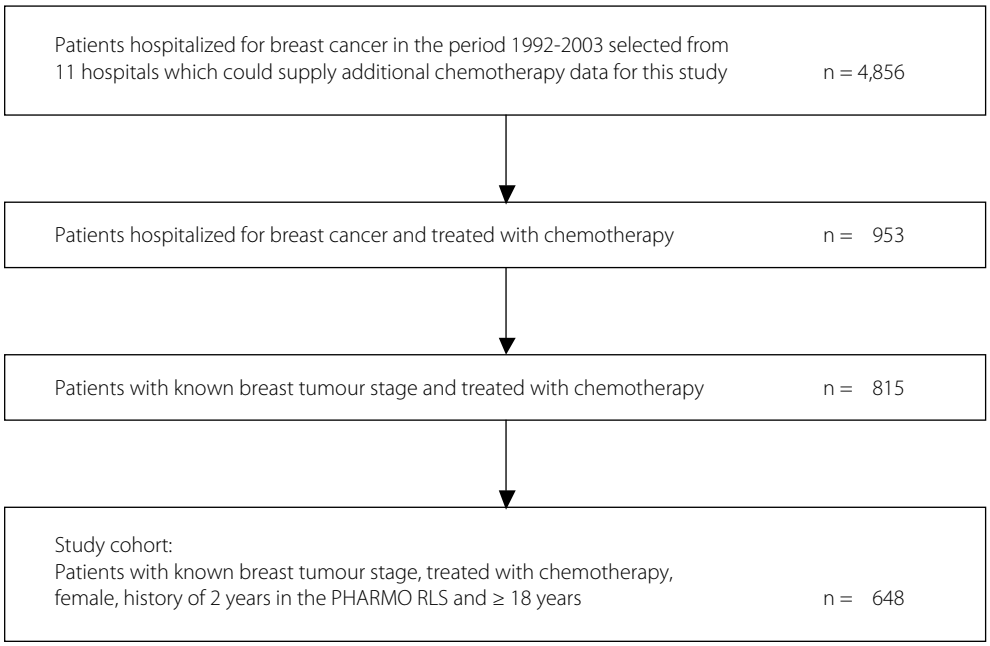

Figure 1. Flowchart of patient selection for the study cohort

Baseline characteristics stratified per cardiotoxic and non-cardiotoxic chemotherapy of patients included in the study cohort are shown in Table 1. Patients who received cardiotoxic chemotherapy compared with patients receiving non-cardiotoxic chemotherapy at cohort

entry date were younger (50 years versus 53 years, respectively; $p = 0.002$), more likely to have started chemotherapy in recent years (68% versus 54% in 2001-2003, respectively; $p < 0.001$), more likely to be diagnosed at stage III (18% versus 6%, respectively; $p < 0.001$) and less likely to be diagnosed at stage IV (5% versus 19%, respectively; $p < 0.001$). For breast cancer therapy two years before the cohort entry date the following can be noted: Patients who received cardiotoxic chemotherapy compared with patients receiving non-cardiotoxic chemotherapy were more likely to undergo radiation therapy (66% versus 44%, respectively; $p < 0.001$), less likely to have received chemotherapy (1% versus 7%, respectively; $p < 0.001$) and more likely to have been hospitalised for breast cancer (86% versus 78%, respectively; $p = 0.017$). Patients who received cardiotoxic chemotherapy compared with patients receiving non-cardiotoxic chemotherapy had experienced less cardiovascular co-morbidities in the two years before the cohort entry date: They less often received anticoagulants/haemostatics (5% versus 11%, respectively; $p = 0.012$) and were less often hospitalized for pre-existing cardiovascular diseases (1% versus 5%, respectively; $p = 0.007$).

Table 1. Characteristics of breast cancer patients at baseline[1]

Characteristics	Total		Chemotherapy				
			Cardiotoxic		Non-Cardiotoxic		
	n	%	n	%	n	%	*p*-value
Characteristics at the cohort entry date[1]							
Total	648	100.0	353	100.0	295	100.0	
Age							0.002
18-39	62	9.6	37	10.5	25	8.5	
40-49	245	37.8	140	39.7	105	35.6	
50-59	193	29.8	108	30.6	85	28.8	
60-69	104	16.0	56	15.9	48	16.3	
70+	44	6.8	12	3.4	32	10.8	
mean ± SD	51.6 ± 10.7		50.4 ± 9.8		53.1 ± 11.5		
Year of cohort entry date[1]							<0.001
1992-1997	79	12.2	24	6.8	55	18.6	
1998-2000	169	26.1	88	24.9	81	27.5	
2001-2003	400	61.7	241	68.3	159	53.9	
Stage of cancer							<0.001
I	99	15.3	49	13.9	50	16.9	
II	392	60.5	221	62.6	171	58.0	
III	81	12.5	64	18.1	17	5.8	
IV	76	11.7	19	5.4	57	19.3	

Characteristics	Total		Chemotherapy				
			Cardiotoxic		Non-Cardiotoxic		
	n	%	n	%	n	%	*p*-value
Breast cancer therapy two years before the cohort entry date[1]							
Prior radiation therapy[2]							<0.001
radiation therapy	158	53.6	83	65.9	75	44.4	
no radiation therapy / unknown	137	46.4	43	34.1	94	55.6	
Prior hormonal therapy	128	19.8	64	18.1	64	21.7	0.276
Prior chemotherapy	25	3.9	5	1.4	20	6.8	<0.001
Prior cardiotoxic chemotherapy	6	0.9	5	1.4	1	0.3	0.228
Prior breast surgery	519	80.1	288	81.6	231	78.3	0.324
Hospitalisations							
breast cancer	533	82.3	302	85.6	231	78.3	0.017
non-breast cancer	8	1.2	3	0.8	5	1.7	0.479
Cardiovascular co-morbidity two years before the cohort entry date[1]							
Severity of cardiovascular co-morbidity							0.188
none/light impact	323	49.8	174	49.3	149	50.5	
moderate impact	176	27.2	105	29.7	71	24.1	
high impact	149	23.0	74	21.0	75	25.4	
Co-medication							
anti-hypertensive drugs	120	18.5	66	18.7	54	18.3	0.919
anti-diabetic drugs	27	4.2	15	4.2	12	4.1	0.998
nitrates	21	3.2	10	2.8	11	3.7	0.657
anti-arrhythmics	2	0.3	0	0.0	2	0.7	0.207
digitalis	3	0.5	1	0.3	2	0.7	0.594
anticoagulants/haemostatics	51	7.9	19	5.4	32	10.8	0.012
lipid lowering drugs	33	5.1	19	5.4	14	4.7	0.858
Hospitalisations							
cardiovascular disease	18	2.8	4	1.1	14	4.7	0.007
diabetes	2	0.3	2	0.6	0	0.0	0.503

[1] Baseline: at and before cohort entry date, the date on which patients received their first chemotherapy, less than two months before or within six months after diagnosis with breast tumour stage III or IV; [2] Information on radiation therapy was only available for 295 patients whose data originated from the Eindhoven Cancer Registry; SD: standard deviation

As the outcomes of this study are cardiovascular events during follow-up, it was determined whether the baseline characteristics: use of anticoagulants/haemostatics and hospitalisation for pre-existing cardiovascular diseases, predicted the type of chemotherapy (cardiotoxic or non-

cardiotoxic) a patient received at baseline. This was performed by using logistic regression by which baseline characteristics that showed statistically significant difference between the two chemotherapy groups (see Table 1), were entered into the multiple logistic regression model. Patients who had been using anticoagulants/haemostatics in the two year period prior to the cohort entry date did not have a significant lower chance to receive cardiotoxic chemotherapy at baseline compared with non-cardiotoxic chemotherapy, after adjustment for possible confounders (odds ratio (OR) 0.74, 95% confidence interval (CI) 0.36, 1.51), while patients who had been hospitalized for cardiovascular diseases in the two years prior to the cohort entry date had a significant lower chance to receive cardiotoxic chemotherapy at baseline than non-cardiotoxic chemotherapy even after adjustment for possible confounders (OR 0.27, 95%CI: 0.08, 0.94).

Table 2. Type of chemotherapy of breast cancer patients at cohort entry and during follow-up

Type of chemotherapy	At cohort entry date		During follow-up			
	First line[1]		Second line		Third line	
	n	%	n	%	n	%
Any chemotherapy	648	100	88	100	28	100
Most frequently used combinations						
CMF	187	28.9	17	19.3	2	7.1
FAC[2]	21	3.2	0	0.0	0	0.0
FEC[2]	153	23.6	9	10.2	0	0.0
AC[2]	149	23.0	22	25.0	4	14.3
EC[2]	25	3.9	4	4.5	2	7.1
Other chemotherapies						
NFL[2]	1	0.2	0	0.0	1	3.6
PH[2]	0	0.0	0	0.0	1	3.6
antracyclines[2]	4	0.6	0	0.0	1	3.6
other chemotherapy[3]	108	16.7	36	40.9	17	60.7
Cardiotoxic chemotherapy						
yes	353	54.5	35	39.8	9	32.1
no	295	45.5	53	60.2	19	67.9

[1] First line treatment: treatment at the cohort entry date; [2] Cardiotoxic chemotherapies; [3] other non-cardiotoxic chemotherapies: cyclophosphamide, methotrexate, taxanes, pyrimidine antagonists, vinka alkaloids; CMF: cyclophosphamide, methotrexate, fluorouracil; FAC: fluorouracil, doxorubicin, cyclophosphamide; FEC: fluorouracil, epirubicin, cyclophosphamide; AC: doxorubicin, cyclophosphamide; EC: epirubicin, cyclophosphamide; NFL; mitoxantrone, fluorouracil, folic acid; PH: paclitaxel, trastuzumab

The type of chemotherapy patients received at the cohort entry date and during follow-up is shown in Table 2. The most frequently used combinations of cytotoxic chemotherapy agents at cohort entry date were CMF (cyclophosphamide, methotrexate, fluorouracil), FEC (fluorouracil, epirubicin, methotrexate) and AC (doxorubicin, cyclophosphamide) of which AC and FEC were considered cardiotoxic. Chemotherapy combinations CMF and AC were also the most frequently used combinations during follow-up. A total of 32 patients not treated with cardiotoxic chemotherapy at cohort entry date received cardiotoxic chemotherapy during follow-up.

The incidence rates of cardiovascular adverse events after one year and total follow-up, stratified by cardiotoxic and non-cardiotoxic chemotherapy, are shown in Table 3. Highest incidence rates of hospital admissions were observed for admissions for cerebrovascular diseases, heart failure and cardiovascular disease admissions other than those classified in Table 3. Highest incidence rates of new cardiovascular drug use were observed for anticoagulants/haemostatics, anti-diabetics and lipid lowering drugs. None of the patients included in the study cohort was admitted for valve disease, hypertensive disease, myocardial infarction or cardiomyopathy, during follow-up.

The overall incidence rate of cardiovascular events during the first year of follow-up based on the first cardiovascular admission or new cardiovascular drug use was 69/1,000 person years (py) for patients treated with cardiotoxic chemotherapy and 98/1,000 py for patients treated with non-cardiotoxic chemotherapy. These incidence rates did not differ significantly: hazard rate (HR) adjusted for age, year of cohort entry date and stage of cancer was 0.74 (95%CI: 0.39, 1.41). The overall incidence rate was 81/1,000 py for patients treated with cardiotoxic chemotherapy and 92/1,000 py for patients treated with non-cardiotoxic chemotherapy for the total follow-up period (HR 0.81, 95%CI: 0.54, 1.20).

A sub analysis was performed in patients with low pre-existing cardiovascular co-morbidity (none/light impact, $n = 323$). The overall incidence rates of cardiovascular adverse events in this sub population were 51/1,000 py (95%CI: 24, 110) for patients treated with cardiotoxic chemotherapy and 55/1,000 py (95%CI: 22, 101) for patients treated with non-cardiotoxic chemotherapy (HR 1.01, 95%CI: 0.35, 2.92). After total follow-up, the overall incidence rates were 65/1,000 py (95%CI: 42, 99) versus 66/1,000 py (95%CI: (41, 97) for patients treated with cardiotoxic chemotherapy and non-cardiotoxic chemotherapy, respectively (HR 0.94, 95%CI: 0.51, 1.73).

Table 3. Incidence rates of cardiovascular events after treatment with chemotherapy in breast cancer patients after one year follow-up and total follow-up

Outcome	Cardiotoxic chemotherapy			Non-Cardiotoxic chemotherapy			Cardiotoxic versus Non-Cardiotoxic	
	Event	Follow-up	Incidence rate	Event	Follow-up	Incidence rate	Hazard ratio	
	n	person years	per 1,000 person years (95% CI)	n	person years	per 1,000 person years (95% CI)	Crude (95% CI)	Adjusted[1] (95% CI)
After one year follow-up								
Any cardiovascular hospitalisation or co-medication	19	274	69.3 (40.0-109.1)	23	234	98.3 (64.1-149.6)	0.70 (0.38-1.29)	0.74 (0.39-1.41)
Any cardiovascular hospitalisation	6	279	21.5 (7.2-46.6)	9	237	38.0 (16.9-71.7)	0.56 (0.20-1.59)	0.63 (0.22-1.87)
heart failure	1	281	3.6 (0.0-21.4)	--	--	--	--	--
cerebrovascular diseases	--	--	--	2	240	8.3 (0.0-29.2)	--	--
other cardiovascular diseases	6	279	21.5 (7.2-46.6)	7	237	29.5 (12.7-59.1)	0.73 (0.24-2.17)	0.77 (0.25-2.41)
Any cardiovascular co-medications	17	275	61.8 (36.4-98.2)	17	236	72.0 (42.4-114.4)	0.85 (0.44-1.67)	0.87 (0.43-1.79)
anti-diabetic drugs	4	279	14.3 (3.6-35.8)	9	238	37.8 (16.8-71.4)	0.38 (0.12-1.23)	0.38 (0.11-1.40)
nitrates	2	280	7.1 (0.0-25.0)	--	--	--	--	--
anti-arrhythmics	--	--	--	1	240	4.2 (0.0-25.0)	--	--
digitalis	1	281	3.6 (0.0-21.4)	--	--	--	--	--
anticoagulants/haemostatics	11	277	39.7 (18.1-72.2)	10	238	42.0 (21.0-75.6)	0.95 (0.40-2.23)	1.10 (0.44-2.73)
lipid lowering drugs	2	281	7.1 (0.0-24.9)	2	240	8.3 (0.0-29.2)	0.86 (0.12-6.09)	0.55 (0.06-5.23)

Outcome	Cardiotoxic chemotherapy			Non-Cardiotoxic chemotherapy			Cardiotoxic versus Non-Cardiotoxic	
	Event	Follow-up	Incidence rate	Event	Follow-up	Incidence rate	Hazard ratio	
	n	person years	per 1,000 person years (95% CI)	n	person years	per 1,000 person years (95% CI)	Crude (95% CI)	Adjusted[1] (95% CI)
After total follow-up								
Any cardiovascular hospitalisation or co-medication	51	632	80.7 (60.1-106.0)	57	621	91.8 (69.2-119.2)	0.87 (0.59-1.27)	0.81 (0.54-1.20)
Any cardiovascular hospitalisation	14	647	21.6 (12.4-35.5)	15	646	23.2 (12.4-38.7)	0.84 (0.41-1.74)	0.90 (0.43-1.90)
angina pectoris	1	661	1.5 (0.0-9.1)	--	--	--	--	--
cardiac disturbances	3	661	4.5 (1.5-13.6)	--	--	--	--	--
heart failure	1	662	1.5 (0.0-9.1)	1	667	1.5 (0.0-9.0)	1.25 (0.07-20.99)	0.67 (0.04-12.23)
cerebrovascular diseases	1	661	1.5 (0.0-9.1)	3	665	4.5 (1.5-13.5)	0.30 (0.03-2.85)	0.41 (0.04-4.32)
disease of arteries	1	661	1.5 (0.0-9.1)	--	--	--	--	--
other cardiovascular diseases	13	648	20.1 (10.8-34.0)	12	648	18.5 (9.3-32.4)	0.98 (0.45-2.16)	1.01 (0.45-2.27)
Any cardiovascular co-medications	45	641	70.2 (51.5-93.6)	50	630	79.4 (58.7-104.8)	0.89 (0.59-1.33)	0.78 (0.51-1.20)
anti-diabetic drugs	11	659	16.7 (7.6-30.3)	19	658	28.9 (16.7-45.6)	0.56 (0.27-1.19)	0.45 (0.20-1.01)
nitrates	5	655	7.6 (3.1-18.3)	3	660	4.5 (1.5-13.6)	1.56 (0.37-6.52)	1.33 (0.31-5.77)
anti-arrhythmics	1	660	1.5 (0.0-9.1)	1	667	1.5 (0.0-9.0)	0.87 (0.05-13.93)	0.73 (0.05-11.67)
digitalis	3	660	4.5 (1.5-13.6)	1	667	1.5 (0.0-9.0)	4.08 (0.41-40.32)	1.83 (0.13-26.43)
anticoagulants/haemostatics	28	646	43.3 (29.4-61.9)	30	646	46.4 (31.0-66.6)	0.92 (0.55-1.54)	0.90 (0.52-1.53)
lipid lowering drugs	9	662	13.6 (6.0-25.7)	13	666	19.5 (10.5-33.0)	0.74 (0.31-1.74)	0.58 (0.24-1.41)

Low number of events resulted in large 95% confidence intervals for the incidence rates and the hazard ratios; 95% CI: 95% confidence interval; [1] Adjusted for age, year of cohort entry date and stage of cancer.

Discussion

This population-based retrospective cohort study showed incidence rates of cardiovascular adverse events among breast cancer patients receiving chemotherapy. The study shows that the overall incidence rates of cardiovascular events during follow-up were around 70-100 per 1,000 person years in daily clinical practice. Incidence rates were similar for patients treated with cardiotoxic or non-cardiotoxic chemotherapy. However, prior to start of chemotherapy, patients who received cardiotoxic chemotherapy were somewhat younger, had received less anticoagulants/haemostatics and were less often hospitalized for cardiovascular diseases than patients treated with non-cardiotoxic chemotherapy.

In this database study, cardiovascular events were based on drug use and hospital admissions, which resulted in an incidence rate of 7-10% per person year in this study cohort. Reported incidences for cardiotoxic events after chemotherapy are in the range of 0.5% to 20% and mostly based on clinical studies.[4, 6, 10, 11] The occurrence of cardiovascular events depends on treatment-related factors such as dose and rate of administration and patient-related factors such as age and pre-existing cardiovascular co-morbidity.[4-8, 10, 11]

Recently, a population-based study by Doyle *et al.* reported a 1.4 times increased risk for heart diseases in patients receiving doxorubicin and a 1.2 times increased risk in elderly patients treated with any chemotherapy compared to no chemotherapy.[16] The increased risk associated with chemotherapy was particularly seen with cardiomyopathy, also resulting in differences between cardiotoxic and non-cardiotoxic chemotherapy. These risks were found in patients 65 years and older and it is known that elderly breast cancer patients have more co-morbidities and thus may be at a particularly high risk of treatment-related cardiotoxicity.[16-21]

Stratification of incidence rates for cardiotoxic and non-cardiotoxic chemotherapy in our study makes it possible to consider both treatment groups separately. The fact that we did not find any differences in incidence rates of cardiovascular adverse events between patients treated with cardiotoxic or non-cardiotoxic chemotherapy, may be explained by the favourable cardiac risk at baseline. Older patients, patients with prior use of anticoagulants/haemostatics or patients with a prior hospitalisation for cardiovascular diseases were less likely to receive cardiotoxic chemotherapy. Though, in a sub analysis in patients with a low cardiac risk at baseline also no differences in incidence rates of cardiovascular adverse events between the two chemotherapy groups were found. Caution is warranted because of low numbers involved. Similar results in incidence rates of the two chemotherapy groups may indicate that also other factors such as rate of administration and cumulative dose were taken into account for the different cytotoxic chemotherapy agents, thereby decreasing the cardiotoxic risk of the treatment.[3-5, 16, 22] Unfortunately, information on dose and rate of administration of chemotherapy were not available in our database. It is most likely that specialists are aware of the risk factors for cardiotoxicity, and take these into account when treating the breast cancer patient. We also found that during follow-up, certain patients switched from non-cardiotoxic to cardiotoxic chemotherapy (11%), which may lead to a reduction in the difference between the two chemotherapy groups. At the same time, some of the patients starting cardiotoxic chemotherapy received non-cardiotoxic chemotherapy as

second-line therapy (8%). We did not investigate the effect of treatment switch on the results.
Radiation therapy has been reported to increase the risk on cardiovascular events.[23, 24] This did not seem to affect the outcomes in our study as patients receiving cardiotoxic chemotherapy compared with patients receiving non-cardiotoxic chemotherapy were more likely to undergo radiation therapy, but did not have significant more cardiovascular events during follow-up. Though, in this study, information on radiation therapy was limited to a subpopulation.
Several limitations of this study need to be addressed. The numbers of patients included in the study are small, therefore stratification of incidence rates of cardiovascular adverse events by baseline characteristic was not appropriate (data not shown). The occurrence of cardiotoxic events were based on drug use and hospital admissions as more detailed information on electrocardiograph (ECG) changes and laboratory values such as left ventricular ejection fraction (LVEF) was not available. Other methods to define cardiotoxic events might have resulted in different incidence rates and also different rates between the two chemotherapy groups. The classification of cardiotoxic and non-cardiotoxic chemotherapy may not be as strict as used in our study, which could lead to a reduction in the difference between the two chemotherapy groups. However, our classification was based on the consultation of a specialist and reflects experience in clinical practice. In addition, anthracyclines are considered the most cardiotoxic agents compared with other cytotoxic chemotherapy agents.[3-6, 8, 9]
Our study was not designed to identify which chemotherapy agents are cardiotoxic, but to provide insight into real-world cardiotoxic and non-cardiotoxic chemotherapy use among breast cancer patients suffering from co-morbidities and the occurrence of incidence of cardiovascular adverse events in clinical practice. With novel agents such as trastuzumab still being potential cardiotoxic and with the aging of the population and the growing number of survivors of breast cancer with co-morbid conditions, adverse events of chemotherapy remain relevant.[8, 25] Therefore, specialists should remain alerted to the risk factors for cardiotoxicity, such as pre-existing cardiovascular disorders, age, dose and rate of administration.
The present population-based cohort study among breast cancer patients receiving chemotherapy showed that the overall incidence rates of cardiovascular adverse events were around 70-100 per 1,000 person years and were similar after cardiotoxic or non-cardiotoxic chemotherapy. Patients with more cardiovascular co-morbidity at baseline received less often cardiotoxic chemotherapy, indicating that specialists took pre-existing cardiovascular diseases into account when treating the breast cancer patient.

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Myocardial infarction, ischaemic stroke and pulmonary embolism before and after breast cancer hospitalisation: a population-based study

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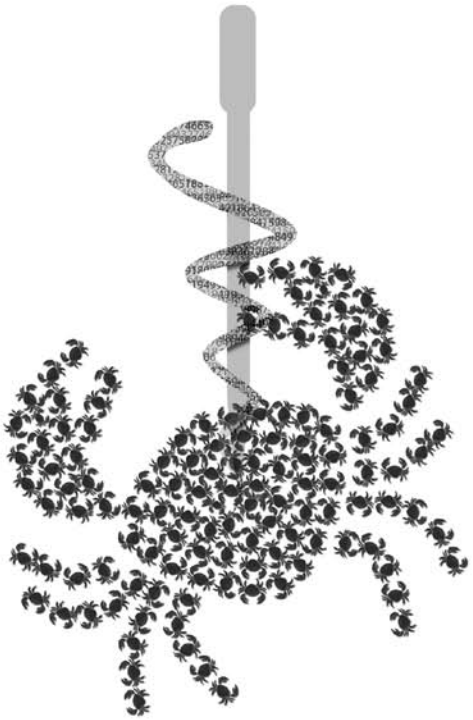

Abstract

Background:
Patients with breast cancer are at increased risk of venous and arterial thrombosis due to cancer itself and its related treatment. Although some studies have assessed the incidence of venous thromboembolism among breast cancer patients, data on the occurrence of specific venous and arterial thrombotic events is scarce.

Objectives:
To study the occurrence of myocardial infarction (MI), ischaemic stroke (IS) and pulmonary embolism (PE) before and after breast cancer hospitalisation compared with cancer-free controls.

Methods:
For this cohort study, women with a first breast cancer hospitalisation during 2000-2007 were selected from the PHARMO Record Linkage System, including drug use and hospitalisations of three million inhabitants in the Netherlands, and matched 1:10 by age to cancer-free controls. The occurrence of MI, IS and PE were assessed in the 12 months before and after breast cancer hospitalisation.

Results:
The analysis included 11,473 breast cancer patients, with a mean (±SD) age of 59 (±14) years. Breast cancer patients were two to three times as likely as their cancer-free controls to have had a hospitalisation for PE, MI or IS in the 12 months before diagnosis, though prevalence was <1% in all groups. Breast cancer patients experienced an extreme high risk of PE in the first six months after diagnosis (Hazard Ratio (HR)=23.5 [95%CI:11.1-49.7] compared to controls), which declined gradually to a four times increased risk (HR=3.6 [95%CI:2.4-5.5]) more than 12 months after breast cancer hospitalisation. However, incidence was low: less than 5 events per 1,000 person years during all time periods. For MI and IS we did not observe significant increased HRs after breast cancer hospitalisation compared to controls.

Conclusions:
Breast cancer patients seem to have a higher risk profile to develop MI and IS, and receive treatment that increases the risk of PE compared to cancer-free controls, although the frequency of hospitalisations was low.

Introduction

The association between cancer and thrombosis, especially venous thrombosis, is well recognized.[1-3] Cancer patients are at increased risk for thromboembolic complications due to the release of pro-coagulants, compression or invasion of blood vessels, or as a result of prolonged immobilization, surgery or treatment with chemotherapeutic agents.[3-6] Several studies suggest that the frequency of thromboembolism in cancer patients, especially PE, is increasing.[6, 7] This is alarming as thrombotic complications among cancer patients are associated with decreased survival.[8, 9]

While the rate of venous thromboembolism among cancer patients has been determined in several retrospective cohort studies,[6-8, 10-14] published epidemiologic data on the incidence of the specific types of venous and arterial thromboembolism[15] is scarce. Moreover, as the risk of thrombosis varies within the cancer patient during the course of malignancy[1] timing of the occurrence of thrombotic events needs further research.

This study focused on the occurrence of specific thromboembolic events in different time intervals among women with a hospitalisation for breast cancer. Although reported rates of venous thromboembolism among breast cancer patients are one of the lowest among cancer patients[6-8], this highly prevalent cancer can contribute significantly to the overall burden of venous thromboembolism[14]. We studied the more serious and well-defined venous and arterial thromboembolic events, which are myocardial infarction, ischaemic stroke and pulmonary embolism. All three will result directly in a hospitalisation and may contribute significantly to the risk of mortality among breast cancer patients. The rates of these three events were determined before and after breast cancer hospitalisation and compared with cancer-free controls. In addition, risk factors for developing myocardial infarction, ischaemic stroke and pulmonary embolism after breast cancer hospitalisation were defined.

Methods

Data source

Data were obtained from the PHARMO Record Linkage System (PHARMO RLS) which consists of multiple observational databases linked on a patient level, covering 3 million inhabitants of geographic defined areas in the Netherlands. Databases relevant for this study include the Dutch National Medical Register (LMR)[16] and the community pharmacy database (out-patient). The hospital records contain detailed information concerning admissions for more than 24 hours and admissions for less than 24 hours for which a bed is required, including primary and secondary diagnoses, procedures and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The drug dispensing histories from community pharmacies contain data on the dispensed drug,

prescriber, dispensing date, amount dispensed, prescribed dose regimens, and thus the duration of use. All drugs are coded according to the Anatomical Therapeutic Chemical (ATC) Classification.

Study population

New hospitalized breast cancer women (ICD-9-CM code: 174) in the period January 1st 2000 to December 31st 2007 were selected from the Dutch National Medical Register of the PHARMO RLS. Date of first breast cancer hospitalisation was defined as the cohort entry date and patients with any cancer hospitalisation (ICD-9-CM codes: 140-239) in the period of ten years before the cohort entry date (or as far as history was available in the Dutch National Medical Register of the PHARMO RLS) were excluded. To be able to define co-morbidities in recent history based on drug use -next to hospitalisations-, patients needed to have at least 12 months of history in the community pharmacy database of the PHARMO RLS. All patients were followed from cohort entry until end of data-collection in the PHARMO RLS (i.e. the patient moves out of the PHARMO RLS catchment area), death, or end of the study period (December 31st 2008), whichever occurred first.

Cancer-free controls

Controls were selected from all women included in the PHARMO RLS; a large, population-based cohort of cancer and cancer-free patients with thorough and unbiased information on medications and hospitalisations. The selection of the control cohort was stepwise. First, for each breast cancer patient we matched randomly 1:20 by age with breast cancer-free women (i.e. never hospitalized for breast cancer (ICD-9-CM code: 174)). Each of these potential controls was assigned the cohort entry date of the cancer patient case match. Second, we eliminated from the pool of 20 possible controls per case, any control that did not have 12 months of history before cohort entry date in the PHARMO RLS and/or who had a hospitalisation with a primary diagnosis for any cancer (ICD-9-CM codes: 140-239) in the period from 10 years before the cohort entry date (or as far as history is available in the Dutch National Medical Register of the PHARMO RLS) until December 31st 2008. Finally, out of the remaining controls that fulfilled the above criteria, ten per case were randomly selected and included in the control cohort.

Outcomes

Only thromboembolic events that are likely to lead to a hospitalisation were included in this study and selected by using primary discharge diagnosis codes: myocardial infarction (ICD-9-CM: 410)[17], ischaemic stroke (ICD-9-CM: 433, 434, 437.1)[18, 19] and pulmonary embolism (ICD-9-CM: 415.1)[20, 21]. These three events were defined in 12 months of history and during follow-up (0 to 6 months, 6 to 12 months and 12 months to total follow-up).

Patient characteristics

The following characteristics were determined: age, duration of follow-up and use of

the following cardiovascular drugs in the year before cohort entry based on ATC codes: platelet aggregation inhibitors (B01AC), other anti-thrombotic drugs (including aspirin, B01A excl. B01AC), lipid-lowering drugs (C10), anti-hypertensives (C02, C03 (excl. C03C), C07, C08, C09 (excl. C09X)), other cardiovascular drugs (e.g. anti-arrhythmics, vasodilators and vasoprotectives; C01, C04, C05) and anti-diabetic drugs (A10). In addition, in the six months after cohort entry we also determined the use of chemotherapy based on hospital discharge diagnoses (ICD-9-CM code: V58.1) and/or oral chemotherapies supplied by community pharmacies (ATC code: L01 excl. targeted drug therapies: L01XC and L01XE), anti-neoplastic hormonal therapy (L02), breast cancer-related surgery (hospital procedure codes: 5-860 to 5-869, 5-870 to 5-879 and 5-400 to 5-409) and cumulative duration of any hospital stay (0-10, >10 days).

Analyses

Prior drug use was compared between breast cancer patients and their controls using the Chi-square test. Prevalence proportions in the 12 months before cohort entry were assessed for each thromboembolic event and expressed with accompanying 95% confidence intervals (CI). Conditional logistic regression was used to calculate odds ratios with 95% CI. For patients with five year history in the PHARMO RLS sensitivity analyses were performed including prevalence proportions in five years before cohort entry. For incidence calculations, patients with a previous event (i.e. myocardial infarction, ischaemic stroke or pulmonary embolism in the 12 months prior to cohort entry) were removed from the at-risk population for that specific event. Incidence rates per 1000 person-years with accompanying 95% CI based on Byar's approximation[22] were calculated for the three distinct periods of follow-up time. Cox proportional hazards regression analysis was used to compare the incidence of the thromboembolic events between breast cancer patients and their cancer-free controls including correction for possible confounders. To visualize the time course of pulmonary embolism among breast cancer patients the proportion of patients with pulmonary embolism (including 95% CI) was determined at 0 to 6 and 6 to 12 months before breast cancer hospitalisation and 0 to 6 and 6 to 12 months after breast cancer hospitalisation among patients with complete follow-up during these four periods. Cox proportional hazards regression models were also fit to identify independent risk factors for developing myocardial infarction, ischaemic stroke or pulmonary embolism in the complete follow-up after hospitalisation for breast cancer. The above mentioned patient characteristics were considered as potential risk factors. All risk factors associated with the outcome in the univariate analyses were included in the multivariate analyses. Statistical significance was defined at an alpha level of 0.05. Data were analysed using SAS (SAS Institute Inc., Cary, NC, USA).

Results

A total of 11,473 women with a first hospitalisation for breast cancer during 2000-2007 was selected from the PHARMO RLS and matched to 114,730 cancer-free women. Mean (±standard deviation: SD) age of patients was 59 (±14) years. The mean (±SD) duration of follow-up was 3.7 (±2.2) years for breast cancer patients and 3.9 (±2.2) years for the cancer-free controls. Use of the various types of cardiovascular drugs and anti-diabetic drugs prior to breast cancer hospitalisation as presented in Table 1 was significantly higher among breast cancer patients compared to their cancer-free controls ($p<0.0001$). Similar use of these drugs was found during the first six months after breast cancer hospitalisation (data not shown). Of the breast cancer patients, 20% received chemotherapy, 32% received anti-neoplastic hormonal therapy and 92% received breast cancer related surgery during or within six months after the first breast cancer hospitalisation. Data on radiation therapy was not available in the PHARMO RLS. Median duration of breast cancer hospitalisation at cohort entry was 2 days (interquartile range=1-5 days).

Table 1. Age and prior drug use of breast cancer patients and cancer-free controls

	Patients with breast cancer (N=11,473)	Cancer-free control cohort (N=114,730)
	N (%)	N (%)
Age in years (mean ± SD)	59 (± 14)	59 (± 14)
Prior drug use [1,2]		
Platelet aggregation inhibitors	1,166 (10)	7,912 (7)
Other anti-thrombotic drugs	524 (5)	2,684 (2)
Lipid-lowering drugs	1,292 (11)	8,765 (8)
Anti-hypertensives	3,914 (34)	23,353 (20)
Other cardiovascular drugs[3]	1,096 (10)	6,270 (6)
Anti-diabetic drugs	808 (7)	4,779 (4)

SD: Standard Deviation; [1]In the 12 months before cohort entry; [2]Results on prior drug use differ significantly between patients with breast cancer and their cancer-free controls ($p<0.0001$); [3]Other cardiovascular drugs, such as anti-arrhythmics, vasodilators and vasoprotectives.

Table 2 presents the proportion of patients with myocardial infarction, ischaemic stroke or pulmonary embolism in the 12 months before breast cancer hospitalisation compared to cancer-free controls. Breast cancer patients were three times as likely as their cancer-free controls to have had a myocardial infarction or pulmonary embolism and two times as likely to have had an ischaemic stroke. However, frequency of events was low: less than 1% in both the breast cancer cohort and their cancer-free controls. Sensitivity analysis including proportions over a period of 5 years before cohort entry showed similar

results, with OR=1.8 (95%CI: 1.3-2.6) for myocardial infarction, OR=1.7 (95%CI: 1.1-2.5) for ischaemic stroke and OR=3.0 (95%CI: 1.7-5.1) for pulmonary embolism.

Table 2. Proportion of patients with myocardial infarction, ischaemic stroke or pulmonary embolism 12 months before breast cancer hospitalisation, compared to a non-cancer population

	Patients with breast cancer (N=11,473)		Cancer-free control cohort (N=114,730)		Odds ratio (OR)
	N	% (95% CI)	N	% (95% CI)	(95% CI)
Myocardial infarction	32	0.28 (0.19-0.39)	112	0.10 (0.08-0.12)	2.9 (1.9-4.2)
Ischaemic stroke	15	0.13 (0.07-0.22)	85	0.07 (0.06-0.09)	1.8 (1.0-3.1)
Pulmonary embolism	11	0.10 (0.05-0.17)	33	0.03 (0.02-0.04)	3.4 (1.7-6.7)

95% CI: 95% confidence interval

Table 3. Incidence rates of myocardial infarction, ischaemic stroke or pulmonary embolism during three periods of follow-up since breast cancer hospitalisation, compared to a non-cancer population

	Patients with breast cancer			Cancer-free control cohort			Hazard Ratio (HR)	
	Event N	Follow-up PY	IR per 1000 PY (95% CI)	Event N	Follow-up PY	IR per 1000 PY (95% CI)	Crude (95% CI)	Adjusted[1] (95%CI)
0 to 6 months after breast cancer hospitalisation								
Myocardial infarction	9	5,497	1.6 (0.7-3.1)	75	55,559	1.3 (1.1-1.7)	1.2 (0.6-2.5)	1.0 (0.5-2.0)
Ischaemic stroke	8	5,505	1.5 (0.5-2.9)	46	55,580	0.8 (0.6-1.1)	1.8 (0.8-3.8)	1.1 (0.5-2.5)
Pulmonary embolism	26	5,506	4.7 (3.1-6.9)	16	55,610	0.3 (0.2-0.5)	17.3 (9.2-32.6)	23.5 (11.1-49.7)
6 to 12 months after breast cancer hospitalisation								
Myocardial infarction	8	5,082	1.6 (0.6-3.1)	60	51,695	1.2 (0.9-1.5)	1.4 (0.7-3.0)	1.5 (0.7-3.1)
Ischaemic stroke	9	5,089	1.8 (0.8-3.3)	39	51,730	0.8 (0.5-1.0)	2.4 (1.1-4.9)	1.8 (0.8-3.9)
Pulmonary embolism	14	5,085	2.8 (1.6-4.5)	15	51,765	0.3 (0.2-0.5)	9.2 (4.4-19.1)	9.0 (4.2-19.5)
12 months to total follow-up after breast cancer hospitalisation								
Myocardial infarction	55	31,360	1.8 (1.3-2.3)	404	334,133	1.2 (1.1-1.3)	1.5 (1.1-2.0)	1.3 (1.0-1.7)
Ischaemic stroke	50	31,438	1.6 (1.2-2.1)	349	334,624	1.0 (0.9-1.2)	1.5 (1.1-2.1)	1.2 (0.9-1.6)
Pulmonary embolism	31	31,430	1.0 (0.7-1.4)	93	335,363	0.3 (0.2-0.3)	3.6 (2.4-5.4)	3.6 (2.4-5.5)

PY: person years; IR: Incidence rate; 95% CI: 95% confidence interval; [1]Hazard Ratio for myocardial infarction adjusted for prior use of anti-thrombotic drugs, lipid-lowering drugs and anti-hypertensive drugs. Hazard Ratio for ischaemic stroke adjusted for prior use of anti-thrombotic drugs, lipid-lowering drugs, anti-hypertensive drugs and other cardiovascular drugs. Hazard Ratio for pulmonary embolism adjusted for prior use of anti-thrombotic drugs, lipid-lowering drugs and other cardiovascular drugs.

Incidence rates of myocardial infarction, ischaemic stroke or pulmonary embolism are presented for three distinct periods of follow-up time (Table 3). The incidence of myocardial infarction and ischaemic stroke among hospitalized breast cancer patients ranged from 1.5 to 1.8 per 1,000 person years (py) for the various follow-up periods.
Compared to the cancer-free control cohort after correction for possible confounders, the hazard ratio (HR) for myocardial infarction was 1.0 (95%CI: 0.5-2.0) in 0 to 6 months, 1.5 (95%CI: 0.7-3.1) in 6 to 12 months and 1.3 (95% CI: 1.0-1.7) in 12 months to total follow-up. For ischaemic stroke these were 1.1 (95%CI: 0.5-2.5), 1.8 (95%CI: 0.8-3.9) and 1.2 (95% CI: 0.9-1.6) respectively. In contrast, the incidence of pulmonary embolism decreased over time from 4.7 per 1,000 py in 0 to 6 months after breast cancer hospitalisation, to 1.0 per 1,000 py in 12 months to total follow-up. Compared to the controls, the risk of pulmonary embolism was largely increased, especially shortly after hospitalisation. In the first six months, the adjusted HR was 23.5 (95%CI: 11.1-49.7), while the HR was 9.0 (95%CI: 4.2-19.5) between 6 to 12 months, and 3.6 (95%CI: 2.4-5.5) 12 months and later after breast cancer hospitalisation. This change in the proportion of breast cancer patients with pulmonary embolism over time is visualized in Figure 1. The proportion of patients with pulmonary embolism increased over time before breast cancer diagnosis, with the highest peak directly after diagnosis and a decrease thereafter.

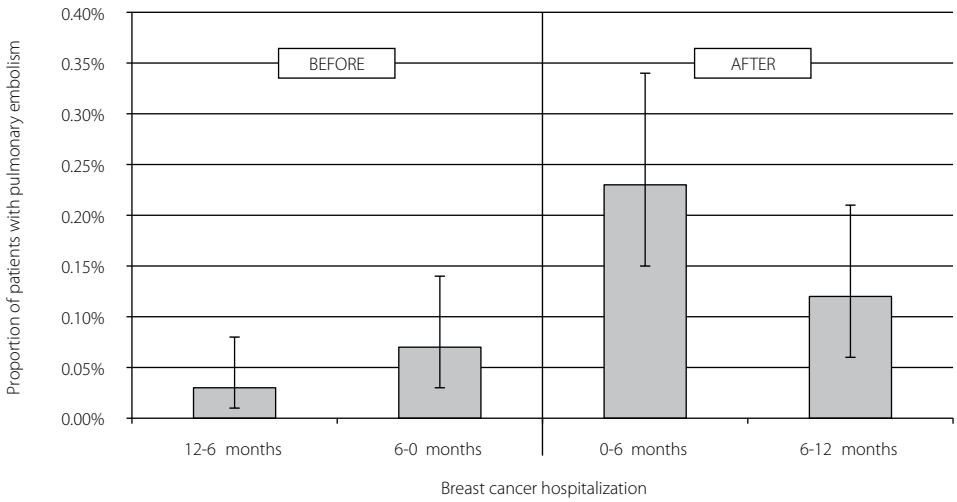

Figure 1. Patients with pulmonary embolism (including 95% confidence intervals) in the 12 months before and 12 months after breast cancer hospitalisation

Multivariate analyses in Table 4 show that independent risk factors for developing myocardial infarction in the complete follow-up after hospitalisation for breast cancer were: older age (≥70 years vs. ≤ 49 years; HR=5.9; 95%CI: 2.0-17.2), prior use of anti-hypertensives (HR=1.6; 95%CI: 1.0-2.8) and cumulative duration of hospital stay longer

than 10 days (irrespective of type of hospitalisation) during the first six months of follow-up (HR=1.6; 95%CI: 1.0-2.6).

Table 4. Risk factors for developing myocardial infarction, ischaemic stroke or pulmonary embolism after hospitalisation for breast cancer

	Myocardial infarction		Ischaemic stroke		Pulmonary embolism	
Characteristics	**HR Multivariate[1]**	**95% CI**	**HR Multivariate[1]**	**95% CI**	**HR Multivariate[1]**	**95% CI**
Age at diagnosis						
≤ 49 years	1	reference	1	reference	1	reference
50-69 years	3.5	(1.2-9.9)	2.5	(0.7-8.6)	2.3	(1.1-4.6)
≥ 70 years	5.9	(2.0-17.2)	5.8	(1.7-20.0)	3.0	(1.3-6.7)
Prior drug use[2]						
Platelet aggregation inhibitors	1.5	(0.8-2.7)	1.9	(1.1-3.4)		
Other anti-thrombotic drugs			1.6	(0.8-3.4)		
Lipid-lowering drugs	1.2	(0.6-2.2)	0.7	(0.4-1.5)		
Anti-hypertensives	1.6	(1.0-2.8)	2.6	(1.4-4.8)		
Other cardiovascular drugs[3]	1.0	(0.5-1.8)	1.0	(0.5-1.9)		
Anti-diabetic drugs	1.7	(0.9-3.2)	2.4	(1.3-4.3)		
Treatment[4]						
Chemotherapy					2.4	(1.3-4.5)
Anti-neoplastic hormonal therapy					2.1	(1.3-3.4)
Duration of any hospitalisation[4]						
0-10 days	1	reference			1	reference
>10 days	1.6	(1.0-2.6)			2.6	(1.6-4.3)

HR: hazard ratio; 95% CI: 95% confidence interval; [1]The multivariate model included all factors that were univariately associated with the outcome; [2]Defined in the 12 months before breast cancer hospitalisation; [3]Other cardiovascular drugs, such as anti-arrhythmics, vasodilators and vasoprotectives; [4]Defined during the first six months after breast cancer hospitalisation.

Independent risk factors for developing ischaemic stroke were: older age (≥70 years vs. ≤ 49 years; HR=5.8; 95%CI: 1.7-20.0) and prior use of platelet aggregation inhibitors (HR=1.9; 95%CI: 1.1-3.4), anti-hypertensives (HR=2.6; 95%CI: 1.4-4.8) or anti-diabetic drugs (HR=2.4; 95%CI: 1.3-4.3). Independent risk factors for developing pulmonary embolism in complete follow-up after correction for other risk factors were: older age (≥70 years vs. ≤ 49 years; HR=3.0; 95%CI: 1.3-6.7), use of chemotherapy (HR=2.4; 95%CI: 1.3-4.5) or anti-neoplastic hormonal therapy (HR=2.1; 95%CI: 1.3-3.4) and total hospital stay >10 days (HR=2.6; 95%CI: 1.6-4.3) during the first 6 months of follow-up.

Discussion

Our large population-based study showed that the proportion of breast cancer patients hospitalized for pulmonary embolism changed remarkably over time. Breast cancer patients were three times as likely as their cancer-free controls to have had a hospitalisation for pulmonary embolism in the 12 months before breast cancer diagnosis. Directly after breast cancer hospitalisation a 24-fold, significant increased risk for pulmonary embolism was found and this risk declined gradually to a four times increased risk for thromboembolism more than 12 months after breast cancer hospitalisation. Regarding arterial thromboembolism, breast cancer patients were three times as likely to have had a myocardial infarction and two times as likely as to have had an ischaemic stroke before breast cancer hospitalisation compared to their cancer-free controls, but we did not observe significant increased hazard ratios after breast cancer hospitalisation.

Similar proportions of venous thromboembolism before breast cancer diagnosis, i.e. 0.06%-0.1%, were found in previous studies.[10, 12] However, in the study of White *et al*., venous thromboembolism rates before breast cancer diagnosis among patients registered in the California Cancer registry were similar to the age-, race- and sex-specific rates in California.[12] A higher incidence of pulmonary embolism in the first six months after breast cancer hospitalisation and decrease in the periods afterwards was also found by Chew *et al*. who reported 1.2 events of venous thrombosis per 100 py during the first half-year and 0.6 per 100 py during the second half-year of follow-up.[11] When taking into account that in the study of Chew *et al*. both deep vein thrombosis and pulmonary embolism were included and that the former occurs two to three times more often than the latter,[6, 7] these incidences of venous thrombosis are similar to ours: 4.7 per 1,000 py in the first half-year and 2.8 per 1,000 py in the second half-year after breast cancer hospitalisation. Chew *et al*. also found a 4-fold higher risk of venous thrombotic events among breast cancer patients in the first year after breast cancer diagnosis compared with the general population.[11]

The increased rate of pulmonary embolism before breast cancer hospitalisation might be caused by the presence of occult cancer.[23, 24] The increased risk of pulmonary embolism directly after breast cancer hospitalisation can be explained by the cancer itself and its related treatment, including surgery, chemotherapy, radiotherapy, or hormone therapy and immobilization following treatment.[3, 4, 13] The low proportion of patients using anti-thrombotic drugs in the first six months after breast cancer hospitalisation (16%) suggests that patients often did not receive thromboprophylaxis after breast cancer hospitalisation. Independent risk factors for developing pulmonary embolism in complete follow-up after correction for other risk factors were: older age and breast cancer treatment-related factors: use of chemotherapy or anti-neoplastic hormonal therapy and total hospital stay of more than 10 days during the first 6 months of follow-up. To our knowledge, there are no previous studies reporting risk factors for solely pulmonary embolism among breast cancer patients. One study reported the following risk factors for developing venous thrombosis, including pulmonary embolism as well as deep vein thrombosis, within

2 years after breast cancer diagnosis: age, the number of chronic co-morbidities and advancing cancer stage.[11] Other studies among various types of cancer found that next to cancer site, the following factors influence the risk of cancer-associated thrombosis: tumour stage, age, gender, co-morbidities (e.g. hypertension, diabetes, obesity and hyperlipidaemia) and cancer treatment (e.g. surgery, radiation therapy, chemotherapy and hormonal therapy)[6, 13, 25].

Regarding arterial thrombotic events, our data suggest that women developing breast cancer are more likely to suffer from cardiovascular co-morbidity: rates of arterial thrombosis before breast cancer diagnosis as well as prior cardiovascular drug use were higher among breast cancer patients than their cancer-free controls. This might be explained by the fact that arterial thromboembolism and breast cancer share similar risk factors such as obesity.[26, 27]

The rate of arterial thrombotic events did not change over time after breast cancer hospitalisation. Risk factors for developing myocardial infarction or ischaemic stroke were prior use of cardiovascular drugs, while chemotherapy or hormonal therapy in the first six months after breast cancer hospitalisation were not significantly related to the risk of developing myocardial infarction or ischaemic stroke. This might be due to the fact that patients are treated less aggressively when cardiovascular co-morbidities are present[28, 29]; therefore, the increased risk of arterial thrombosis after chemotherapy, or anti-neoplastic hormonal therapies which is seen in other studies,[30-33] was not seen in our study.

Our study has some limitations that need to be discussed. First of all, we used a hospitalisation database to identify venous and arterial thromboembolic events. Using an administrative database to define these events is less accurate than clinical chart review. However, we included in our study only the more serious and well-defined venous and arterial thromboembolic events that lead to a hospitalisation[17-21]. We did not include e.g. deep vein thrombosis as many of these patients might be treated outside the hospital,[34] resulting in an underestimation of the incidence of deep vein thrombosis when using hospitalisation data. Another limitation is that we were not able to include risk factors such as tumour stage, radiation therapy, obesity, positive family history of coronary artery disease, cigarette smoking and increased psychological distress, as these were not recorded in the used databases. We could have retrieved data on tumour stage and radiation therapy for a subset of patients[35]. However, as the incidence of thromboembolism among breast cancer patients is low, the sample size was too small to study these risk factors for myocardial infarction, ischaemic stroke and pulmonary embolism separately. Furthermore, our population was restricted to patients hospitalized for breast cancer. Validation of a sub-cohort by linking the PHARMO RLS and the Eindhoven Cancer Registry[35] showed more than 95% of the patients diagnosed with breast cancer in the Netherlands to have been hospitalized. The small proportion of patients that are not hospitalized and therefore not in our current study population are more likely to be 80 years or older, have metastatic breast cancer and are institutionalized.

To achieve optimal treatment and prognosis among breast cancer patients, this study

contributes to the awareness of the incidence of thromboembolic events among breast cancer patients and the risk factors and risk periods of thrombosis. Breast cancer patients seem to have a higher risk profile to develop arterial thromboembolism and receive treatment that increases the risk of venous thromboembolism. However, incidence of hospitalisations for myocardial infarction, ischaemic stroke and pulmonary embolism was low.

Acknowledgements

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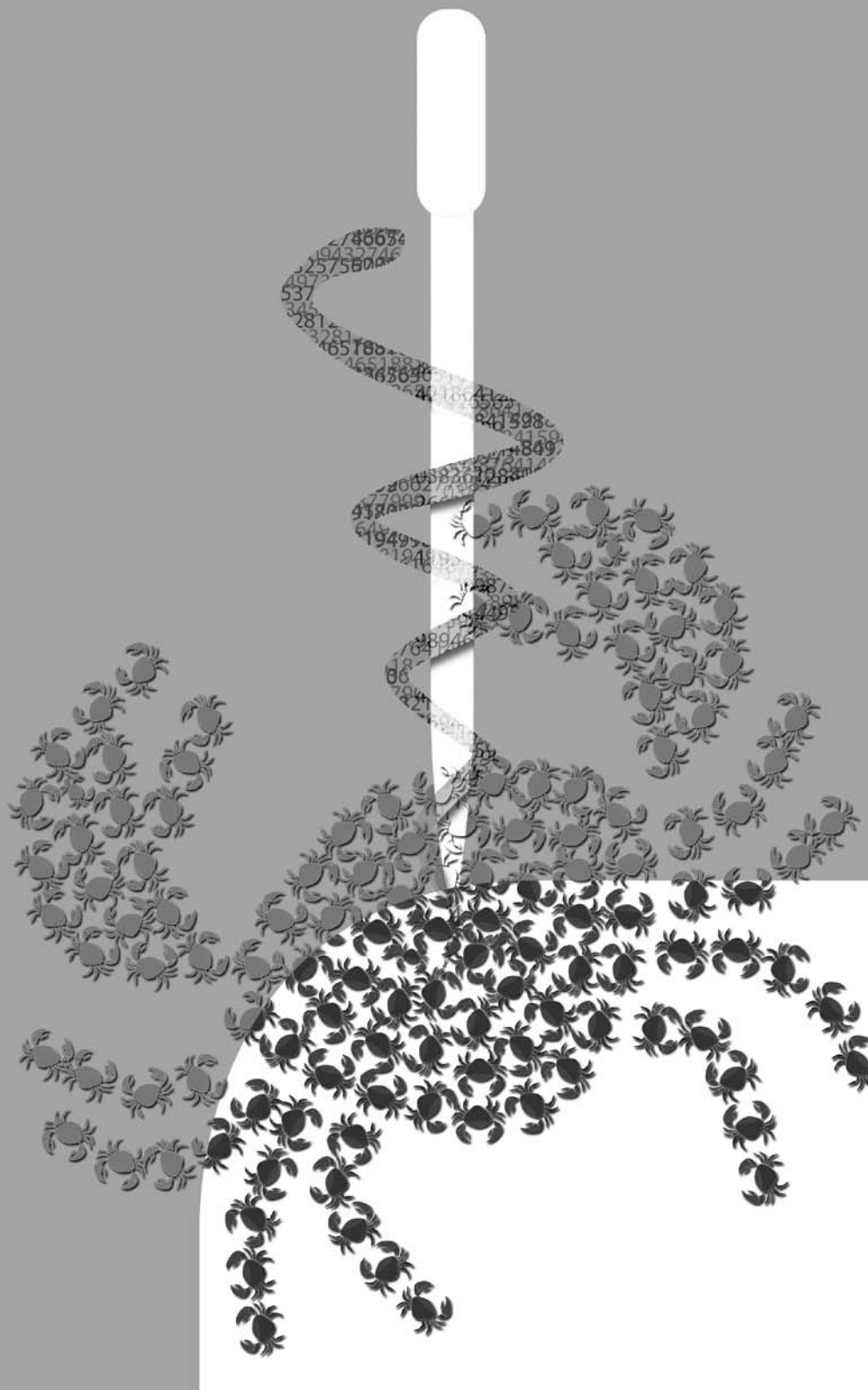
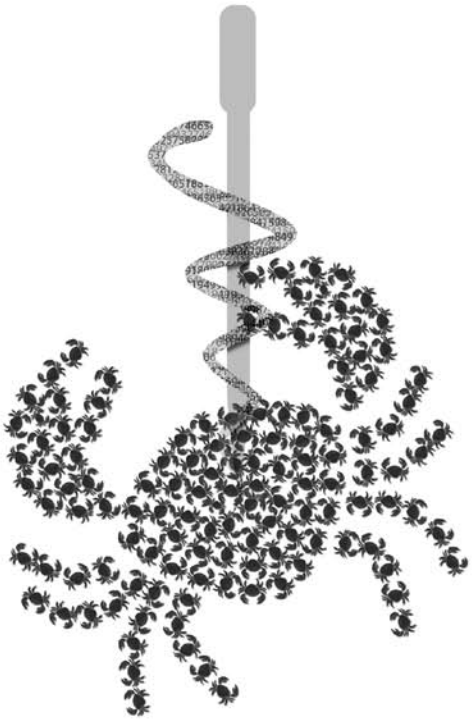


CHAPTER 8 OVERVIEW, DISCUSSION AND CONCLUSION

8.1 Introduction



Introduction to the discussion

The primary aim of this thesis was to create a new data source that enables pharmacoepidemiological studies in the area of oncology. For this, a linkage was created between the Eindhoven Cancer Registry (ECR) and the PHARMO Record Linkage System (PHARMO RLS). In **Chapter 2.3** we showed that this probabilistic record linkage was feasible and valid. The new ECR-PHARMO cohort includes tumour information (such as tumour histology, grade and stage) of incident cancers obtained from the ECR and data on, among other things, drug treatment (out-patient and in-patient), hospitalisations, and clinical laboratory measurements obtained from the PHARMO RLS. In this thesis we focused on the most frequent cancer among women: breast cancer. We presented studies possible using solely the data from the ECR (**Chapter 3**), or the PHARMO RLS (**Chapter 7**). Whereas the added value of both databases combined was described in **Chapter 4, 5 and 6**. The choice of data source (the ECR, PHARMO RLS or the ECR-PHARMO cohort) for a specific research depends on the research question and study design.
Before discussing the results of the studies on systemic breast cancer treatment, and the studies on new morbidities after breast cancer diagnosis and treatment, we address the uniqueness of the data available in the ECR-PHARMO cohort. For this, the ECR-PHARMO linkage is set out against other comparable database linkages available in Northern America and Europe. Finally, we will end the discussion with a section on future perspectives.

8.2 Record linkage for pharmacoepidemiological studies in cancer patients

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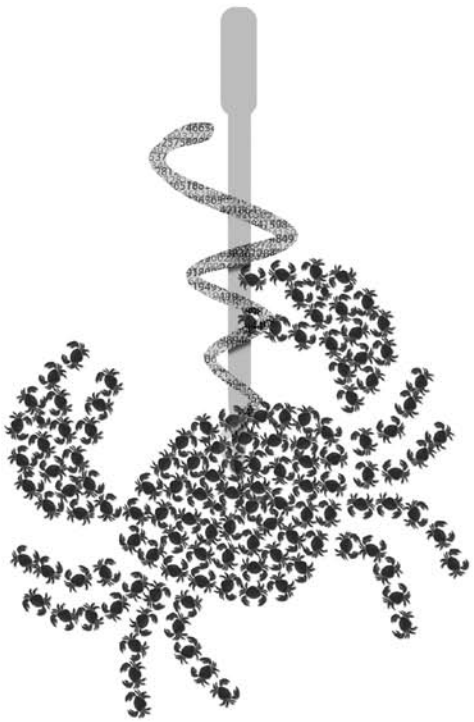
Pharmacoepidemiology and Drug Safety 2011, in press



Abstract

Background:
An increasing need has developed for the post-approval surveillance of (new) anti-cancer drugs by means of pharmacoepidemiology and outcomes research in the area of oncology.

Objectives:
To create an overview that makes researchers aware of the available database linkages in Northern America and Europe which facilitate pharmacoepidemiology and outcomes research in cancer patients.

Methods:
In addition to our own database, i.e. the Eindhoven Cancer Registry (ECR) linked to the PHARMO Record Linkage System, we considered database linkages between a population-based cancer registry and an administrative healthcare database that at least contains information on drug use and offers a longitudinal perspective on healthcare utilization. Eligible database linkages were limited to those that had been used in multiple published articles in English language included in Pubmed. The HMO Cancer Research Network (CRN) in the US was excluded from this review, as an overview of the linked databases participating in the CRN is already provided elsewhere. Researchers who had worked with the data sources included in our review were contacted for additional information and verification of the data presented in the overview.

Results:
The following database linkages were included: the Surveillance, Epidemiology, and End-Results–Medicare; cancer registry data linked to Medicaid; Canadian cancer registries linked to population-based drug databases; the Scottish cancer registry linked to the Tayside drug dispensing data; linked databases in the Nordic Countries of Europe: Norway, Sweden, Finland and Denmark; and the ECR-PHARMO linkage in the Netherlands. Descriptives of the included database linkages comprise population size, generalizability of the population, year of first data availability, contents of the cancer registry, contents of the administrative healthcare database, the possibility to select a cancer-free control cohort, and linkage to other healthcare databases.

Conclusions:
The linked databases offer a longitudinal perspective, allowing for observations of health care utilization before, during, and after cancer diagnosis. They create new powerful data sources for the monitoring of post-approval drug utilization, as well as a framework to explore the (cost-)effectiveness of new, often expensive, anti-cancer drugs as used in everyday practice.

Introduction

In recent years there has been an enormous growth in the number of new anti-cancer agents being investigated and approved for the treatment of cancer[1]. While effectiveness and safety of these new therapies are thoroughly studied in randomized clinical trials, little data are available on these parameters in everyday clinical practice. Effectiveness of anti-cancer drugs may be different than expected as daily practice differs from the experimental setting with respect to the heterogeneity of patients, their age, treatments and comorbidity. Moreover, important safety issues may not be detectable in clinical trials since the frequency of many adverse events is low and adverse effects of cancer therapies may occur many years after drug administration[2,3]. With the ageing of the population, the increasing survival of cancer patients, and the often accelerated FDA (US Food and Drug Administration) and EMA (European Medicines Agency approval of new anti-cancer drugs, pharmacoepidemiological studies in the area of oncology are increasingly important.

Therefore, maybe even more important than for most other drugs, systems that facilitate post-approval drug utilization and (cost-)effectiveness studies on anti-cancer drugs should be in place. Cancer registry data linked to administrative healthcare databases, such as medical claims databases or electronic medical records, make this type of research in cancer patients possible. Data from cancer registries contain important information (such as tumor histology, grade and stage) necessary to analyze the treatment and safety of a particular cancer treatment in a certain group of cancer patients. Data from administrative healthcare databases contain information on treatment of the cancer itself and other morbidities, including data about the type of drug or combination of drugs and/or treatment modalities, duration of treatment, and dosage. With medical record linkage of both data sources a new valuable source is created which can be used to shed light on the burden of cancer, disease management, safety aspects, comorbidity patterns and outcomes assessments, and follow-up of patients before and after cancer diagnosis in routine daily practice.

In this article we will give an overview that can serve to make researchers aware of the various database linkages available that contain the abovementioned information. The linked databases include 1) a cancer registry and 2) an administrative healthcare database that includes information on drug use, preferably with information on morbidity other than cancer. Moreover, we discuss their unique potential for post-approval surveillance of anti-cancer drugs.

Cancer registries linked to administrative healthcare databases

In this overview we restrict consideration to existing database linkages in Northern America and Europe that have been used in multiple published articles that can be retrieved via Pubmed. As our focus is to provide databases that allow studies on cancer treatment and its related outcomes, we only included cancer registry data linked to administrative healthcare databases that at least contain information on drug use and possible data on other morbidities during follow-up. Not included are potential sources in non-English literature, those not (yet) described in published literature, or those not used for scientific purposes. Researches who have worked with the included data sources were contacted for verification and additional information.

The identified data sources and most important aspects of these linked databases for safety and outcomes research in cancer patients are presented in Table 1. We determined what type of characteristics these databases had with respect to the facilitation of pharmacoepidemiology studies, such as population size, ability to select cancer-free control groups, and linkage to other databases. While it is beyond the scope of this paper to describe the linked databases in detail, a brief description of the source population, the contents of the cancer registries and the administrative healthcare databases, including information on drug use and other clinical outcomes, are described below.

Included linked data sources

The most extensively described database includes the SEER (Surveillance, Epidemiology, and End-Results)-Medicare linked database[4-6] in the US. Other US claims databases that have been linked to cancer registry data are Medicaid databases of which only the North Carolina (NC) Central Cancer Registry (CCR) linked to the NC Medicaid Claims[7-9] is included in Table 1 as a representative example. Others include, for example, cancer registries that participate in the SEER program linked to Medicaid databases, such as the California Cancer Registry linked to California Medicaid[10] and the Metropolitan Detroit Cancer Surveillance System linked to the Michigan Medicaid data[11]. Three examples of cancer registries linked to administrative healthcare databases located in Canada are the British Columbia (BC) linked Cancer Registry and Health data[12, 13], the Saskatchewan Health Plan Databases[14-16] and Manitoba Health databases[17-19]. Of the latter two, only the Saskatchewan Health Plan Databases are included in Table 1 as similarities exist between Saskatchewan and Manitoba (both have similar health care data recording processes, including large, longitudinal, administrative health care utilization databases that include all residents of the province), however, prescription drug and cancer services data were used more often in studies using the Saskatchewan databases[20, 21]. Other good examples of cancer registries linked to administrative healthcare databases are found in the Nordic Countries of Europe: Norway[22, 23], Sweden[24, 25], Finland[26, 27] and Denmark[28-31]. In the rest of Europe two other good examples are the Scottish cancer registry linked to the Health Informatics Centre (HIC) drug dispensing database[32-34] and the Eindhoven Cancer Registry

Table 1. Features of examples of database linkages between a cancer registry and an administrative healthcare database in Northern America and Europe

	Northern America - United States	
	SEER-Medicare	**North Carolina#**
Linkage		
Using	Matching algorithm of social security number, first and last name, dates of birth and death, and sex.	Matching algorithm of social security number, first and last name, date of birth, and county of residence
Availability of data since**	1991	1998
Source population		
Population covered	26% of the US population***	9.4 million
Inclusion and generalizability of the population	Only elderly (≥65 years), persons with end-stage renal disease and some disabled	Only low-income and one of the following: ≥65 years, blind or disabled, pregnant or parent of a child <19
Content of cancer registry	the SEER program	NC Central Cancer Registry (CCR)
Patients diagnosed with a new primary tumor	Yes	Yes
Information on patient and primary tumor characteristics	Yes	Yes
Information on first course of treatment (e.g. surgery, radiotherapy, chemotherapy (yes/no))	Yes	Yes
Vital status	Yes	Yes
Content of administrative healthcare database including information on drug use and comorbidity	Medicare claims database	NC Medicaid claims database
Pharmacy dispensing or prescriptions: (co-)medication	Claims data for covered healthcare services*	Claims data for covered healthcare services*
Data on type of chemotherapeutics	Yes; sensitivity of claims data varies by the agent	Yes; sensitivity of claims data varies by the agent
Information on comorbidity	Yes; claims data for covered healthcare services*	Yes; claims data for covered healthcare services*
Other information		
Cancer-free control cohort	Yes	Yes
Linkage to other healthcare databases	Yes; e.g. US Census Bureau, physicians' claims	Yes; e.g. US Census Bureau, US Social Security Master Death File
Additional information$	http://healthservices.cancer.gov/seermedicare; Study example, see[52]	http://www.schs.state.nc.us/SCHS/CCR/ and http://www.cms.gov/home/medicaid.asp; Study example, see[53]

SEER: Surveillance, Epidemiology and End Results; **Date represents the start date of one of the two linked databases that started the most recent with data collection; ***From 2000 onwards, the following population-based cancer registries are part of the SEER program: Alaska Native Tumor Registry, Arizona Indians, Los Angeles, San Francisco-Oakland, San Jose-Monterey, Greater California, Connecticut, Detroit, Atlanta, Rural Georgia, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, Seattle-Puget Sound and Utah; *Claims data for covered healthcare services, including hospital, physician, outpatient, home health and hospice bills; $ Web pages last accessed on 13 May 2011; # Serves as an example of a cancer registry linked to Medicaid.

Table 1. Features of examples of database linkages between a cancer registry and an administrative healthcare database in Northern America and Europe (continued)

	Northern America - Canada	
	British Columbia	**Saskatchewan**
Linkage		
Using	Internal personal identifier	Unique health service number (HIRF registration number)
Availability of data since**	1980	1976
Source population		
Population covered	4.2 million	~ 1 million
Inclusion and generalizability of the population	Only cancer patients	Excluding drug beneficiaries of another government agency (<10%)
Content of cancer registry	BC Cancer Agency	Cancer Registry
Patients diagnosed with a new primary tumor	Yes	Yes
Information on patient and primary tumor characteristics	Yes	Yes
Information on first course of treatment (e.g. surgery, radiotherapy, chemotherapy (yes/no))	Yes	Yes
Vital status	Yes	Yes, through death certificates and hospital reports
Content of administrative healthcare database including information on drug use and comorbidity	BC Cancer Agency pharmacy database	Prescription drug plan database
Pharmacy dispensing or prescriptions: (co-)medication	No; only anti-cancer drugs	Yes
Data on type of chemotherapeutics	Yes	No
Information on comorbidity	Not routinely available	Yes; via Saskatchewan Health Hospital File
Other information		
Cancer-free control cohort	No	Yes
Linkage to other healthcare databases	No	Yes; e.g. hospitalizations, medical services
Additional information$	http://www.bccancer.bc.ca; Study example, see[54]	http://www.saskcancer.ca/ and http://www.health.gov.sk.ca/drug-plan-benefits; Study example, see[55]

**Date represents the start date of one of the two linked databases that started the most recent with data collection; $ Web pages last accessed on 13 May 2011.

Table 1. Features of examples of database linkages between a cancer registry and an administrative healthcare database in Northern America and Europe (continued)

	Europe - Nordic countries of Europe	
	Norway	**Sweden**
Linkage		
Using	Unique personal identity number*	National registration number
Availability of data since**	2004	2005
Source population		
Population covered	4.9 million	9.2 million
Inclusion and generalizability of the population	Nationwide	Nationwide
Content of cancer registry	Cancer Registry of Norway	Swedish Cancer Registry
Patients diagnosed with a new primary tumor	Yes	Yes
Information on patient and primary tumor characteristics	Yes	Yes
Information on first course of treatment (e.g. surgery, radiotherapy, chemotherapy (yes/no))	Yes	No
Vital status	Yes, via linkage with Statistics Norway	Yes, via linkage to the causes of death register
Content of administrative healthcare database including information on drug use and comorbidity	Norwegian Prescription Database (NorPD) based on all dispensed drugs from pharmacies	Prescribed drug register or data of pharmacy dispensings
Pharmacy dispensing or prescriptions: (co-)medication	Yes	Yes
Data on type of chemotherapeutics	No; drug use in-hospital is not recorded	No; drug use in-hospital is not recorded
Information on comorbidity	Yes; via Norwegian Patient Register and via indication for prescribing (from 2009 onwards)	Yes; via hospitalization data
Other information		
Cancer-free control cohort	Yes	Yes
Linkage to other healthcare databases	Yes; e.g. Medical birth registry (MBRN), causes of death registry	Yes; e.g. In-Patient Registry, causes of death registry
Additional information$	http://www.kreftregisteret.no/ and www.nhv.se/norpen; Study example, see[56]	http://www.socialstyrelsen.se/register/halsodataregister/cancerregistret/ and www.nhv.se/norpen; Study example, see[57]

*Currently there are ongoing projects including linkage between Norwegian prescription database and cancer registry, however not yet published; **Date represents the start date of one of the two linked databases that started the most recent with data collection; $ Web pages last accessed on 13 May 2011.

Table 1. Features of examples of database linkages between a cancer registry and an administrative healthcare database in Northern America and Europe (continued)

	Europe - Nordic countries of Europe	
	Finland	**Denmark**
Linkage		
Using	Unique personal identification number	Central person registration number
Availability of data since**	1993	1990
Source population		
Population covered	5.3 million	5.5 million/ 1.2 million, 1.7 million
Inclusion and generalizability of the population	Nationwide	Nationwide/ Regional databases are representative for the Danish population
Content of cancer registry	Finnish Cancer Registry	Danish Cancer Registry
Patients diagnosed with a new primary tumor	Yes	Yes
Information on patient and primary tumor characteristics	Yes	Yes
Information on first course of treatment (e.g. surgery, radiotherapy, chemotherapy (yes/no))	Yes	Yes
Vital status	Yes, via the Finnish Cancer Registry or Statistics Finland	Yes, via linkage with the Death Registry or registration in cancer registry
Content of administrative healthcare database including information on drug use and comorbidity	Reimbursed pharmacy dispensings from Social Insurance Institution	National Register of Medicinal Product Statistics, OPED or PDNJ
Pharmacy dispensing or prescriptions: (co-)medication	Yes	Yes
Data on type of chemotherapeutics	No; drug use in-hospital is not recorded	No; drug use in-hospital is not recorded
Information on comorbidity	Yes; via hospitalization data	Yes; via hospitalization data
Other information		
Cancer-free control cohort	Yes	Yes
Linkage to other healthcare databases	Yes; e.g. Statistics Finland for date and cause of death	Yes; e.g. Danish Patient Registry
Additional information$	http://www.cancer.fi/syoparekisteri/ and www.nhv.se/norpen; Study example, see[58]	http://www.cancer.dk/Epi+Research/ and www.nhv.se/norpen; Study example, see[59]

OPED: Odense university Pharmacoepidemiology Database; PDNJ: Pharmacoepidemiology Prescription Database in Northern Jutland; **Date represents the start date of one of the two linked databases that started the most recent with data collection; $ Web pages last accessed on 13 May 2011.

Table 1. Features of examples of database linkages between a cancer registry and an administrative healthcare database in Northern America and Europe (continued)

	Europe - Western Europe	
	Scotland	**Southeastern Netherlands**
Linkage		
Using	Community Health Index Number	Probabilistic linkage of gender, date of birth, 1st initial, 1st letter and soundex code of last name, first 4 characters of zip code
Availability of data since**	1989	1998
Source population		
Population covered	~ 400,000	~ 1 million
Inclusion and generalizability of the population	Demographic breakdown and health status of Tayside resembles the rest of Scotland	Representative for the Southeastern Netherlands
Content of cancer registry	Cancer Registration Database (SMR 6)	Eindhoven Cancer Registry
Patients diagnosed with a new primary tumor	Yes	Yes
Information on patient and primary tumor characteristics	Yes	Yes
Information on first course of treatment (e.g. surgery, radiotherapy, chemotherapy (yes/no))	Yes	Yes
Vital status	Yes, via linkage with the General Register Office	Yes, via linkage to the death registry of the Central Bureau of Genealogy
Content of administrative healthcare database including information on drug use and comorbidity	Health Informatics Centre (HIC) drug dispensing database	PHARMO Record Linkage System
Pharmacy dispensing or prescriptions: (co-)medication	Yes	Yes
Data on type of chemotherapeutics	No; drug use in-hospital is not recorded	Yes; via in-hospital pharmacy
Information on comorbidity	Yes; via hospital admission database (SMR1)	Yes; via ECR: comorbidity at diagnosis and via PHARMO RLS: hospital database
Other information		
Cancer-free control cohort	Yes	Yes
Linkage to other healthcare databases	Yes; e.g. maternity admissions; mental health admissions	Yes; e.g. clinical lab, general practitioners, pathology (PALGA)
Additional information$	http://www.isd.scot.nhs.uk/isd/3535.html and http://www.dundee.ac.uk/hic; Study example, see[60]	http://www.ikcnet.nl and http://www.pharmo.com; Study example, see[61]

SMR: Scottish Morbidity Record; **Date represents the start date of one of the two linked databases that started the most recent with data collection; $ Web pages last accessed on 13 May 2011.

(ECR) linked to the PHARMO Record Linkage System[35, 36]. A description of the data included in these database linkages is presented in Table 1.
Next to the database linkages included in Table 1, the HMO Cancer Research Network (CRN) in the US also includes cancer registries linked to administrative healthcare databases[37-40]. An overview of the contents of the healthcare systems participating in the CRN, including size of the population, available data sources and year of availability, can be found in previous published articles[37, 38]. The CRN consists of the research programs and enrollee populations of 14 integrated health systems, including Group Health Cooperative, Harvard Pilgrim Health Care, Henry Ford Health System/Health Alliance Plan, HealthPartners Research Foundation, Lovelace Health System, Fallon Community Health Plan, Geisinger Health System, Marshfield Clinic/Security Health Plan and Kaiser Permanente in six regions: Colorado, Georgia, Hawaii, Northwest (Oregon and Washington), Northern California, and Southern California. Collectively, these organizations provide care to nearly 11 million individuals.[37, 39] Cancer registries are in place at 11 of the CRN systems and all systems have electronic databases that contain information on enrollment, demographics, outpatient pharmacy, outpatient visit claims, and hospitalization claims.[37, 38] Laboratory, pathology, radiology procedures and death data will also be incorporated.[37] Research studies might either be conducted including all the CRN systems or within the individual CRN member systems.

Source population

When performing research with a cancer registry linked to an administrative healthcare database, it is important to define the population covered by both databases to be able to determine the generalizability and heterogeneity of the data. The numbers of patients covered in each linked database included in this overview are described in Table 1. Most databases cover all age categories and are either nationwide or representative for the total population covered in a country or state. However, the BC cancer agency covers only new patients with cancer and cancer-free patients are not included[12, 13]. The US-based sources cover selected populations due to the restrictions of the claims data. For example, the SEER-Medicare only includes patients ≥65 years, and patients <65 years who are disabled or have end-stage renal disease.[4, 6] The NC CCR linked to the NC Medicaid Claims only includes patients who have a low-income and are ≥65 years, blind, disabled, pregnant, or the parent or caretaker of a child who is younger than 19 years[8]. Due to the selected populations most investigators have focused their analysis on patients ≥65 years[6]. For types of cancers that predominate among elderly patients, like lung, colorectal, breast and prostate cancer, the databases can provide a comprehensive sample of the cancer population, but for other malignancies, such as testicular cancer, leukemia and lymphoma, the databases provides a more limited insight.[6]

Cancer registries

Cancer registries included in this review all record information of newly diagnosed

cancer patients including patient characteristics and information on the primary tumor such as histology, stage, or grade. Information on the initial course of treatment directly after diagnosis (e.g. surgery, chemotherapy and radiotherapy) is also included in all cancer registries except for the Swedish cancer registry[24]. The ECR of the Southeastern Netherlands is the only cancer registry that since 1995 also includes routinely available information on comorbidity at diagnosis obtained from the clinical record by trained registry personell.[36, 41] Other registries might obtain this information from linkage to other healthcare databases or via additional data collection.

Cancer registries often do not register clinical information on disease progression as this is very time consuming. Date of death and sometimes cause of death is mainly used as the final outcome. However, as for research purposes longitudinal information on the progress of cancer is often desirable, several actions are undertaken to obtain this information. First of all, data on cancer relapse can be registered additionally for a specific study[42]. Second, data can be obtained by linkage to other healthcare databases such as pathology (biopsy confirmed recurrences) and/or hospitalization data[43]. Finally, clinical algorithms might be developed to identify cancer relapse. For example, if there is a gap between chemotherapy or radiotherapy administration and treatment is started somewhere during follow-up, it might be assumed that this was for relapsed disease[44]. Such a clinical algorithm can only be used if almost all patients are treated shortly after relapse. A check should assure that a second primary cancer has not developed, e.g. by using data from the cancer registry. Moreover, patients with cancer relapse will be missed if they relapsed very quickly after diagnosis or if they did not opt for any treatment, e.g. because of coexisting illness, or poor performance status.

Information on drug use

Administrative healthcare databases included in this review all contain information on drug use. Prescription and pharmacy dispensing databases include information on drug use for various indications. These databases can be used to study drug treatment before cancer diagnosis (e.g. to measure preexisting morbidities that might influence decisions on the treatment of cancer) and drug treatment of a patient after cancer diagnosis, including the drug treatment of other morbidities. However, the prescription and pharmacy dispensing databases of Saskatchewan, the Nordic countries and Scotland do not record the drugs dispensed to individuals during a hospital stay. This means that drug treatment of cancer and other morbidities for which the patient is hospitalized are not recorded, creating possible observation gaps[45]. Whether the two US medical claims databases (Medicare and Medicaid), also include drugs supplied for various indications before cancer diagnosis depends on the covered services[6, 8].

Administrative healthcare databases that include information on the drug treatment of cancer to study patterns of cancer care should be divided into those that include information on oral anti-cancer drugs and those that include information on intravenously administered chemotherapy. While most community pharmacies include information on

oral anti-cancer drugs, such as hormonal treatment for breast cancer[46], administrative healthcare databases that include data on intravenous chemotherapy for the treatment of cancer are less common. The pharmacy database of the BC Cancer Agency is unique as this database includes all chemotherapeutic agents that are provided by the same centralized pharmacy[13]. However, this database only includes information on anti-cancer drugs and does not include drugs of these patients supplied for other indications[12, 13]. The only administrative healthcare database in Table 1 that includes both prescriptions that have been dispensed by community pharmacies as well as in-hospital pharmacies (including chemotherapeutics) is the PHARMO RLS[36]. Having data of both data sources facilitates studies on total cancer treatment of a patient including oral anti-cancer drugs via data from the community pharmacies, and/or intravenously administered chemotherapeutics via data from the in-hospital pharmacies.

Longitudinal information on chemotherapy administration in the US located databases was recently evaluated. When comparing automated clinical data on chemotherapy in the CRN systems with medical charts, the sensitivity was good (89.5%)[47]. The sensitivity of the Medicare claims to identify persons undergoing chemotherapy was comparable to that of the CRN (≥88%). However, with respect to identifying specific agents in the Medicare claims, the sensitivity varied by the specific drugs used to treat a cancer type[48].

Information on other clinical outcomes

To study the long-term outcomes of cancer patients after initial cancer care, longitudinal information on health care utilization of cancer and other morbidities is needed. Medical claims databases contain not only medical claims on drug use but also medical claims on, for example, hospitalizations, cancer tests, and procedures[6, 8, 37]. This results in a high variety of studies that are possible with these data[4, 39]. For the prescription and pharmacy dispensing databases, information on morbidities is often obtained via linkage to hospitalization data.

All existing database linkages can be enriched by new healthcare databases, such as clinical laboratory data or medical birth registries, ad hoc collected data on variables not available in the databases, as well as detailed clinical data and biosamples. These data can additionally be linked to the existing databases in the same way as the current linkages are performed, creating even more research possibilities.

Opportunities for post-approval surveillance of anti-cancer drugs

The record-linkage of a cancer registry and a longitudinal healthcare database creates new opportunities for postapproval evaluation of anti-cancer drugs. The cancer registry data provide detailed tumor information of incident cancer patients, which is not possible to derive from other databases such as medical claims data, hospitalization data, or data from general practices,[49] whereas the administrative healthcare databases offer a

longitudinal perspective, making it possible to look at healthcare utilization before, during and after cancer diagnosis. First of all, data on drug use and comorbidities before cancer diagnosis can be used to measure preexisting morbidities that might influence decisions on the treatment of cancer. Secondly, data on drug use directly after cancer diagnosis can be used to study the pattern of cancer care: the precise type of chemotherapeutics administered as initial treatment, but also as follow-up treatment or palliative care. Finally, data on drug use and comorbidities after cancer diagnosis and treatment can be used to monitor the effectiveness and safety of cancer treatments. Whether the linked databases are a good data source for all these types of studies depends on the size of the underlying population and the specific data available in the separate data sources. Besides monitoring the effectiveness and safety of cancer treatments, these databases also allow the study of the relationship between drug use and the risk of cancer[32, 50].

The strengths and limitations of the separate existing databases are maintained after linkage. The additional value of the linkage itself is that it greatly improves the utility of existing healthcare databases for pharmacoepidemiological research in the area of oncology. Retrieving the data on drug use and comorbidities via linkage to an administrative database instead of additional data collection, has the following advantages. Data from administrative healthcare databases are available at relatively low cost and pharmacoepidemiological studies with these data can often be conducted with little delay. These databases allow continuous post-approval surveillance of drug dissemination and drug effects, the two core elements of pharmacoepidemiology. Their representativeness of routine clinical care makes it possible to study real-world effectiveness. As administrative healthcare databases automatically register all interventions, the adverse drug reactions that were not anticipated via results from clinical trials are still recorded and can be evaluated. However, one must keep in mind that only the complications that require an intervention are recorded, which mostly includes the more severe and acute events. Another advantage is that linkage to a longitudinal healthcare database allows the selection of a cancer-free control cohort. This creates the opportunity to compare the rate of developed morbidities in cancer patients following cancer treatment with the rate of morbidities found in the general population and it allows the study of the relationship between drug use and the risk of cancer. Finally, administrative healthcare databases often cover large populations, which will shorten the time necessary to identify a sufficient number of users of a newly marketed drug. However, the population required to detect an association between a particular anti-cancer drug and adverse event depends upon the type of event, the proportion of patients using the drug, the homogeneity of the population (specific cancer type and disease stage), the previous received anti-cancer treatments, and the magnitude of the risk. For monitoring the effectiveness and safety of new cancer treatments the size of the cohorts are often too small as new targeted drugs are merely administered in patients with a specific disease stage (advanced disease), concurrently or in specified sequential regimens with the traditional cytotoxic agents. However, by combining the linked data sources as presented in Table 1, large enough study populations may soon become available.

If the research question and study design lend themselves to utilize one of the described linked databases as a data source, it is the responsibility of the investigator to consider the strengths and weaknesses in deciding whether to use the linked database for their research. Procedures to obtain data from a linked database vary depending on the data source. Release of the data is generally project specific and the project must first be approved before data can be obtained, as is the case when requesting SEER-Medicare data. However, in contrast to the longstanding SEER-Medicare data, in most cases a researcher will need to get permission from both the cancer registry and the pharmacoepidemiology database separately as technically, the data belong to different data providers. Moreover, not all databases provide direct access to the datasets. For example, the Scottish HIC drug dispensing database and the Dutch ECR-PHARMO cohort only provide data directly to (local) scientists, while for e.g. pharmaceutical companies, local researchers would work with these private companies in developing the research question and design, performing the analysis and providing the results. Regarding the Nordic prescription databases, data can be accessed as previously described[45] and knowledge exchange, research and training of the various databases is facilitated via the Nordic Pharmacoepidemiological Network (NorPEN)[51]. In Table 1 websites are presented that provide additional information on the process of accessing the data from the different databases. Researchers can contact the concerning database(s) and submit an application for the required data including information on the funding source. Timelines of getting permission for obtaining the data and accessing the data very much depend on what type of data the researcher is seeking and whether, next to the linked database, also data from other healthcare databases are needed. Other conditions on using the data, such as security of the data, are also determined for each data source separately. Finally, a researcher must be familiar with the data sources and understand how the individual databases were generated, before using the linked databases for their research.

Conclusion

For the post-approval surveillance of (new) anti-cancer drugs there is an increasing need for detailed data on cancer diagnosis, drug use and other morbidities from representative populations with lengthy follow-up. Due to this demand, the linkage of cancer registry data with other clinical data is a rapidly evolving field across the world. In this brief overview we gave examples of existing database linkage initiatives in Northern America and Europe including a cancer registry and an administrative healthcare database that at least includes information on drug use and comorbidities. Currently, many new database linkages are initialized and we recognize that the list provided in this overview is not exhaustive; it is simply a starting point. This overview can serve to make researchers aware of the various valuable sources of information available to study the disease management of cancer including safety aspects, comorbidity patterns and outcomes assessments. An

emerging field in which these new databases play an important role is the ability to serve as a tool to raise hypotheses and allow for certain (cost-) effectiveness approaches of new, often expensive, anti-cancer drugs in the context of cancer care in community-based settings.

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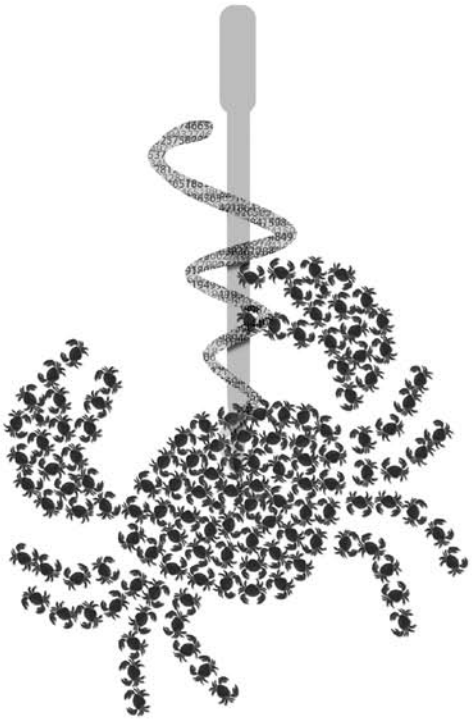
8.3 General discussion of breast cancer studies



General discussion of breast cancer studies

In this thesis the current treatment patterns of anti-cancer drugs in patients with breast cancer as well as the new morbidities that may occur after breast cancer diagnosis and treatment were addressed. Both the observed treatment and new morbidities may be different than expected from clinical trials due to the heterogeneity of patients, their age, co-morbidity, co-medication and treatment compliance.

Systemic breast cancer treatment

In **Chapter 3** it was shown that the use of adjuvant systemic treatment for patients with early stage breast cancer increased significantly over time, from 37% during 1990-1997, to 53% of all breast cancer patients in 2002-2006. This increase was especially seen for patients with node-negative breast cancer. The growing number of breast cancer patients receiving anti-cancer drugs stresses the need for more pharmacoepidemiology in the field of oncology. Its role is to provide population-based evidence that, added to evidence obtained from randomized controlled trials, would support the decision making process of clinicians when treating the breast cancer patient.

Regarding chemotherapy, we observed a large variety in the types of chemotherapeutic agents administered to breast cancer patients (**Chapter 4**). While patients receiving chemotherapy in the adjuvant setting were in general treated according to the guidelines, there was a large variation in the palliative setting, probably due to the high variability in individual presentation. Information on the administration of chemotherapy in everyday clinical practice is especially important for the drugs that are currently allowed on the Dutch list of high-cost medicines (e.g. trastuzumab and bevacizumab)[1]. As these drugs are currently temporary admitted on this list, the Dutch government will allow 80% reimbursement. However, effectiveness research for these drugs is needed in order to determine if the drugs should definitively be allowed on the list and the subsequent special reimbursement rule[2]. For this, more insight into the administration of trastuzumab and bevacizumab in daily practice is needed, which is provided in the current study. Though, a larger cohort of breast cancer patients receiving these drugs is required to be able to perform effectiveness research.

Regarding adjuvant hormonal therapy, the major concern is continuation of treatment. Without this information, the effect of a drug cannot be interpreted realistically. Again, a population-based setting is needed to determine true rates of discontinuation as patients appear to discontinue their medications at higher rates in practice settings than in clinical trials[3]. For example, the proportion of breast cancer patients discontinuing hormonal therapy in randomized clinical trials is reported to be 10-28% depending on the length of follow-up,[4-6] whereas in our study, 51% of the patients followed for five years discontinued

this therapy (**Chapter 5**). This early discontinuation of hormonal therapy in daily practice is reported to be associated with increased mortality[7]. The exact risk is difficult to assess in a population-based setting as factors related to treatment discontinuation (adverse events) might also be associated with the increased risk of mortality. However, the results of population-based studies can serve as a tool to generate hypotheses for clinical trials.

New morbidities after breast cancer diagnosis and treatment

With the number of prevalent breast cancer patients increasing considerably, many more individuals will be undergoing cancer treatment, coping with progressive disease, or living cancer-free after diagnosis and treatment. For this reason, it becomes increasingly important to determine morbidities that occur after breast cancer diagnosis and treatment and eliminate those that are chronic and irreversible. As side effects of breast cancer treatment may not always be detectable in clinical trials, post-approval evaluation of treatments in daily practice is essential. In this thesis addressed whether the multidisciplinary approach to treat breast cancer generated new morbidities.

The risk of morbidity associated with treatment for breast cancer depends on, among other things, the type of treatment administered. Cardiotoxicity of certain chemotherapeutics is well recognized[8]. When specialists are aware of the risk factors for cardiotoxicity, such as pre-existing cardiovascular morbidity or increased age, patients will be less likely to receive cardiotoxic chemotherapy or adaptations will be made in dose and rate of administration. The results of our study support this as we did not find a difference in incidence of cardiovascular morbidity between patients who underwent cardiotoxic or non-cardiotoxic chemotherapy **(Chapter 6)**. However, in this study 648 patients were included with a median follow-up of 1.5 years, while cardiotoxicity may occur many years after anthracycline administration[9]. Future studies including longer follow-up time should determine the incidence of late cardiac abnormalities after anthracyclines.

Another well-recognized morbidity associated with the treatment of breast cancer is thrombosis[10]. In our study we determined the more serious venous and arterial thromboembolic events using hospitalisation data to define myocardial infarction, ischaemic stroke and pulmonary embolism **(Chapter 7)**. While the incidence of these events was less than 1%, recognition of patients at-risk is important as outcomes included might be fatal and patients may survive longer in absence of these morbidities[11,12]. Due to this low expected incidence we selected the largest breast cancer cohort possible by using, instead of the linked ECR-PHARMO cohort, only the data from the PHARMO RLS. This more than doubled the cohort size, however, resulted in not having information on radiation therapy and tumour stage; with radiation therapy being associated with myocardial infarction[13] and metastatic disease being a risk factor for developing thromboembolic disease[14]. An enlargement of the ECR-PHARMO cohort in the future is needed to allow studies on rare events after breast cancer diagnosis and treatment without loss of information.

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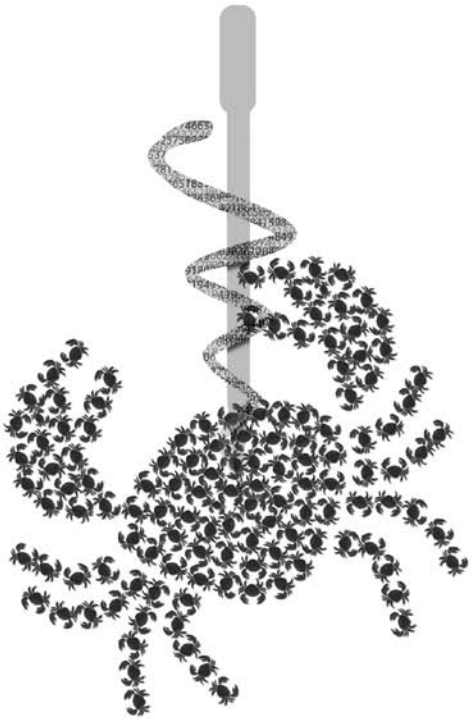
8.4 Future perspective



Future perspective

This thesis demonstrated a new data source for pharmacoepidemiology and outcomes research in the area of oncology: the linked Eindhoven Cancer Registry (ECR) and PHARMO Record Linkage System (PHARMO RLS). In this chapter we discuss whether the new created ECR-PHARMO cohort is representative for the Dutch population, the current data limitations of the linked cohort and possible ways to overcome these limitations in the future. Moreover, we want to present the various valuable sources of information available in the ECR-PHARMO cohort, and the many other types of studies possible, next to those presented in this thesis. Finally, we discuss important aspects for continuation of this cohort in the future, including data confidentiality, governance and research ethics.

Representativeness of ECR-PHARMO cohort

Cancer patients included in the linked ECR-PHARMO cohort were representative for those included in the total ECR **(Chapter 2.3)**. However, we showed that patients who were linked were slightly older and were diagnosed with the more common tumour types compared to the total ECR. This may reflect a need, ability and willingness of younger patients and the patients with uncommon tumours, to travel further to receive treatment not emphasized in their local area (non-academic hospitals). Moreover, the linkage ran more efficiently when patients were diagnosed more recently. This might be explained by time dependent linkage variables (e.g. zip code) that have changed in one of the two registries over time, hindering linkage in the older years.

The ECR itself is fairly representative for the total Dutch population. However, the incidence of cancer may vary within the regions of the Netherlands due to differences in exposure to risk factors, interventions for early detection (screening) or the characteristics of the underlying population[1]. The region covered by the ECR (southeastern Netherlands) does not contain academic or specialized cancer hospitals, does not include one of the top three largest cities in the Netherlands, includes fewer immigrants compared to the western Netherlands, and the population is somewhat older than the total Dutch population[2]. However, extrapolation of patient numbers to the Netherlands is possible as well as (inter)national comparison of cancer incidence as incidence rates can be age-standardised to the standard European population (European Standard Rate [ESR]).

Data limitations

A limitation of the ECR-PHARMO cohort is the current cohort size. For monitoring the effectiveness and safety of new cancer treatments the size of the current cohort is too small: new targeted drugs are merely administered in patients with a specific disease stage

(advanced disease), concurrently or in specified sequential regimens with the traditional cytotoxic agents, resulting in a small study population of cancer patients to begin with. Detecting an association between a rare adverse event and a particular anti-cancer drug administered to a homogeneous group of cancer patients is therefore impossible using the current cohort.

Another limitation is the fact that the PHARMO RLS records only complications that require an intervention, which mostly includes the more severe and acute events. This especially accounts for the hospitalisation database which only registers hospital admissions for more than 24 hours and admissions for less than 24 hours for which a bed is required. Additionally, for hospitalisations, primary diagnoses are mainly used in research, as it is difficult to distinguish whether secondary diagnoses are complications or prevalent co-morbidities. Regarding the pharmacy data, a general problem using dispensing data to assess drug use is that we do not know if and when the dispensed drugs are actually ingested by the patients. Moreover, the community and in-hospital pharmacy database do not include information on the indication of treatment. In the near future the PHARMO general practitioner database will be linked to the ECR-PHARMO cohort, making it possible to look at less severe co-morbidities and indication of drug use. Finally, drugs used by patients in nursing homes are not (completely) recorded in the PHARMO RLS. The same is observed in the ECR, with outpatients with a clinical diagnosis only (no pathological diagnosis), generally not recorded by the cancer registry. However, this systematic under registration is limited (<2%) and the ECR is considered to be more than 95% complete[3].

Expansion of the ECR-PHARMO cohort

Expansion of the ECR-PHARMO cohort in the near future is of utmost importance for research in study cohorts of less frequent cancer types, specific disease stages, or for patients with a specific cancer treatment. Of course, the ECR-PHARMO cohort will expand after every annual update, resulting in a longer follow-up of existing cancer patients and including new incident cancer patients, but, this increase will not be immense. Moreover, more data of recent cancer patients are needed if we want to study the use of new anti-cancer drugs.

At the time of the first ECR-PHARMO linkage, linkage was performed for patients who were diagnosed with cancer in the period 1998-2006 **(Chapter 2.3)**. Since then, a second linkage was performed adding 2007 and 2008. At that time, the ECR and the PHARMO RLS collected data of more than 2 and 3 million inhabitants, respectively, with only 45% of the catchment areas (approximately 1 million inhabitants) overlapping. Currently, the PHARMO Institute is stimulating pharmacists, general practitioners and others to share their data needed to expand the data collection of its databases in the region of the ECR, resulting in a larger overlap between the ECR and PHARMO RLS as presented in Figure 1.

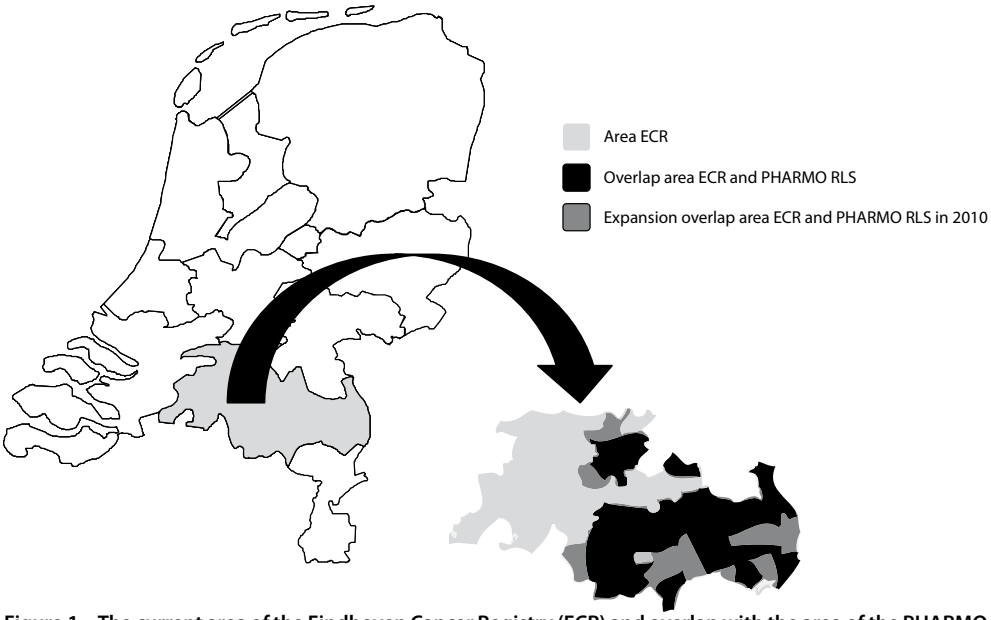


Figure 1. The current area of the Eindhoven Cancer Registry (ECR) and overlap with the area of the PHARMO record linkage system (PHARMO RLS) and expansion of this area in 2010.

This increased overlap does not comprise all databases included in the PHARMO RLS. It currently includes the community pharmacy database and the national databases linked to the PHARMO community pharmacy database such as the Dutch National Medical Register. Expansion of the other PHARMO databases (e.g. in-hospital pharmacy, clinical laboratory data and general practitioner data) as well as further expansion of the community pharmacy database is needed for complete overlap of the ECR and PHARMO RLS. With this, the overlap region will be doubled from approximately 1 million to 2.4 million inhabitants. However, this still will not be enough for the study of rare cancers and rare adverse events, but it will increase the research possibilities for the more common cancers.

Next to expansion of the data collection of the PHARMO RLS, the data from the cancer registry can be expanded by adding data from another regional cancer registry, or using data from all eight Dutch regional cancer registries: the Netherlands Cancer Registry[4, 5]. Currently, if a specific study question requires a larger cohort of cancer patients linked to e.g. the PHARMO community database, other national databases that include information on cancer diagnosis are used such as the Dutch National Medical Register **(Chapter 7)** or the Dutch nationwide network and registry for histo- and cytopathology (PALGA)[6, 7]. However, expansion of the cancer registry data is preferred as both the Dutch National Medical Register and PALGA do not contain detailed tumour information (such as stage) necessary to analyse the treatment and safety of a particular cancer treatment in a certain group of cancer patients.

Although expansion might be possible from a technical point of view, it also requires the willingness and the trust to participate of a wide variety of caregivers and institutions: those hosting the data. Such participation is guided by the focus of both the ECR and the PHARMO RLS; that data are collected primarily not for science but to support caregivers (e.g. medical specialists, general practitioners and pharmacists). For this, information is provided as feedback on a regular basis. A close cooperation between caregivers and researchers is essential as caregivers will assure adequate interpretation of the study results. The construct of the current ECR-PHARMO cohort took several years of negotiations, data cleaning and creating the right governance to cooperate and to secure the continuity of the linkage systems.

Research possibilities using the ECR-PHARMO cohort

Cancer surveillance covers the spectrum from primary prevention to end-of-life care. The linkage between the ECR and the PHARMO RLS creates a new unique source for numerous types of studies related to cancer control (Figure 2).

Before cancer diagnosis	Treatment of cancer	Follow-up after cancer diagnosis and treatment	Death
Pre-existing morbidities and the risk of cancer	Pattern of cancer care	Follow-up treatment, palliative care	Survival
Drug use and the risk of cancer	Pharmacogenetics for personalized medicine	Patient reported outcomes	
	Morbidities that influence the treatment of cancer	Late effects of treatment	
	Drug–drug interactions	Disease progression	
	Acute adverse events		

Figure 2. From cradle to grave: pharmacoepidemiology and outcomes research in the area of oncology using the ECR-PHARMO cohort

Before cancer diagnosis

In this thesis we gave an example of the assessment of pre-existing morbidities (e.g. myocardial infarction, ischaemic stroke or pulmonary embolism) before breast cancer

hospitalisation and determined whether the prevalence of these morbidities was higher compared to cancer-free controls **(Chapter 7)**. Future studies may have as primary objective to determine whether certain morbidities increase the risk of cancer such as hepatitis C infection and hepatocellular carcinoma,[8] or diabetes and the risk of cancer[9].
Studies on drug use and the risk of cancer were not included in this thesis as this concerns another major topic, that of pharmacovigilance. Next to the fact that certain drugs may increase the risk of cancer, other existing drugs might have unforeseen benefits and decrease cancer risk. Examples of studies in both fields that can be performed with data from the ECR-PHARMO cohort are: cancer occurrence after the use of anti-diabetics[10], non-steroidal anti-inflammatory drugs (NSAIDs)[11, 12], or statins[6, 13]. The additional value of using cancer registry over hospitalisation or general practitioner data as outcome database is that it provides the identification of all incident patients, which is not possible using the other two databases[14]. Future studies can use the ECR-PHARMO linkage to determine the relationship between drug exposure and the risk of cancer.

Treatment of cancer

Regarding pattern of cancer care, data on the initial treatment (e.g. surgery, chemotherapy, hormonal therapy and radiotherapy) can be extracted from the ECR, while follow-up treatment, detailed information on e.g. the type of anti-cancer drugs and the duration of use can be retrieved from the in- and outpatient pharmacy database of the PHARMO RLS. In this thesis we gave two examples of treatment pattern studies: the type of chemotherapy and endocrine treatment used by patients with breast cancer **(Chapter 4 and 5)**. With expansion of the in-hospital pharmacy database of the PHARMO RLS presenting the various chemotherapy regimens for smaller cancer cohorts will become possible as well as for the larger cancer cohorts presenting the various chemotherapy regimens by for example nodal status and age, and taking performance status and socio-economic status into account.
The ECR-PHARMO cohort can be used to determine treatment patterns and outcomes of patients whose genetic profile has been assessed, as has been done in previous studies using the PHARMO RLS[15, 16]. Pharmacogenetics is studying the interindividual differences in drug response at the genetic basis to achieve personalized drug therapy. In studies using the ECR-PHARMO data it can be determined why some patients respond well to cancer therapy and others do not[17].
Whether co-morbidities at the time of diagnosis influence the cancer treatment received by cancer patients can be determined with data from solely the ECR[18, 19] as this registry includes information on co-morbidity at diagnosis obtained from the clinical record[20, 21]. However, next to evaluating whether a patient with co-morbidities receives a certain treatment yes or no, changes in chemotherapy such as dose delays, dose reductions, early discontinuation, or excluding a specific cytostatic, may, among other things, be based on the presence of co-morbidities[22]. To study whether the choice in type of cytotoxic agents varies when co-morbidities are present, data from the in- and outpatient pharmacy data

from the PHARMO RLS can be used. In our study on cardiovascular events in breast cancer patients receiving chemotherapy, we hypothesized that the similar results in incidence rates of the cardiotoxic and non-cardiotoxic chemotherapy groups may indicate that specialists took pre-existing cardiovascular diseases into account when choosing the type of chemotherapy administered to the breast cancer patient **(Chapter 6)**. This can be determined in a future study assessing whether patients with present (cardiac) co-morbidity do not receive specific cytostatics such as anthracyclines followed by taxanes, as advised in the Dutch guidelines[23]. Moreover, studies on co-morbidities and early discontinuation can be performed using data from the ECR-PHARMO cohort. Unfortunately, studies on dose delays or dose reductions are more difficult as dose is not available for all data obtained from the in-patient pharmacies.

Related to the influence of co-morbidities on the treatment of cancer is the effect of the medications for other morbidities on the outcome of systemic cancer treatment. Data from the ECR-PHARMO cohort can be used to provide insight in the prevalence of potential drug–drug interactions between anti-cancer drugs and non anti-cancer drugs[24]. Moreover, it can be studied whether concurrent use of co-medication and anti-cancer drugs leads to reduced effectiveness of the anti-cancer drugs[17].

Studies on acute adverse events directly influencing the cancer treatment can be performed in the ECR-PHARMO cohort using e.g. clinical laboratory data. Study examples that can be performed with data from the ECR-PHARMO cohort are: assessing myelotoxicity, anaemia and neutropenia in cancer patients who underwent chemotherapy[25], or determining the values of serum liver biochemical tests (i.e. albumin, alanine aminotransferase, aspartate aminotransferase, bilirubin and gamma glutamyl transpeptidase) in patients with cancer during chemotherapeutic treatment[26].

Follow-up after cancer diagnosis and treatment

The in- and out-patient pharmacy data and the hospitalisation data of the PHARMO RLS can be used to determine treatment after initial cancer care. For example, in our study on chemotherapy in breast cancer patients **(Chapter 4)** we determined administration of palliative chemotherapy after initial adjuvant treatment by assuming that restart of chemotherapy after 90 days indicated a distant recurrence as secondary adjuvant chemotherapy for the treatment of a local recurrence is not recommended[27]. Another example is switching endocrine treatment during follow-up as we presented in our study on treatment continuation of endocrine treatment in breast cancer patients **(Chapter 5)**.

The ECR-PHARMO cohort can serve to select cancer patients with certain characteristics to be included in a population-based cross-sectional survey. This has been done in previous studies using data from the ECR.[28, 29] In this way the data from the ECR-PHARMO cohort can be enriched via information obtained from questionnaires, such as long-term health-related quality of life, diet and smoking habits, adverse drug reactions, and treatment compliance.

Late effects of treatment and their costs can be evaluated with the data from the ECR-PHARMO RLS by using, for example, the hospitalisation database of the PHARMO RLS. As all hospitalisations are automatically registered in this administrative database, the hospitalisations related to e.g. adverse drug reactions that were not anticipated via results from clinical trials are still recorded and can be evaluated. However, one must keep in mind that the hospitalisation database records only the more severe and acute morbidities that require a hospital admission for more than 24 hours and admissions for less than 24 hours for which a bed is required. Less severe and more chronic conditions might be captured by using the dispensed medications included in the PHARMO out-patient pharmacy. This thesis presented two studies in which the morbidities of breast cancer patients after diagnosis and treatment were determined using the hospitalisation and out-patient pharmacy database of the PHARMO RLS **(Chapter 6 and 7)**. Moreover, in future studies less severe events can be captured via the PHARMO general practitioner database. Outcome studies assessing adverse events of specific chemotherapeutic agents administered to cancer patients might be possible in the near future after expansion of the ECR-PHARMO cohort, and more specifically, the in-hospital pharmacy database of the PHARMO RLS. This is important as with the increasing number of new agents being investigated and approved for treatment of patients with breast cancer and the increasing number of breast cancer patients living cancer-free after diagnosis and treatment, the long-term toxicity profiles of new anti-cancer drugs come into focus.

Studies on disease progression have been performed by the ECR with data retrieved via additional registration of local recurrences and metachronous metastases from the clinical record based on a periodical active or passive follow-up[30-32]. However, data on disease progression can also be obtained via the ECR-PHARMO cohort. For example, biopsy confirmed recurrences can be obtained via the Dutch National Pathology Registry (PALGA), as the PHARMO RLS is also linked to this database.[33, 34] Next to this, data on recurrences can be obtained via the PHARMO hospitalisation database[17]. Moreover, specifically for prostate cancer, the PHARMO clinical laboratory database might be used for surveillance of patients with localized prostate cancer via PSA (prostate-specific antigen) measurements[35]. Finally, clinical algorithms might be developed to determine cancer relapse. For example, if there is a gap between administration of chemotherapy or radiotherapy and treatment is started somewhere during follow-up, it might be assumed that this was for relapsed disease[36]. Such a clinical algorithm can only be used if almost all patients are treated shortly after relapse and when second primary cancer are excluded by using data from the cancer registry.

Death

Finally, studies on survival after cancer diagnosis can be performed using the ECR-PHARMO cohort. This has been done in many previous published studies using the data from the ECR, with information on vital status obtained from the municipal registers and the Central Bureau for Genealogy[37-39].

Data confidentiality and governance

The ECR is governed and regulated by the Comprehensive Cancer Centre South (CCCS) and the PHARMO RLS by the PHARMO Institute. With governance we refer to the set of rules and regulations that secure the continuity of the individual data sources. The main concern is to guarantee optimal use of the data thereby maintaining confidentiality of patients as well as data providers and registration holders. To ensure confidentiality of personal information, first of all, the PHARMO Institute collects only non-directly patient identifiers such as gender, date of birth and zip code, which are used in the linking process. In the ECR direct patient identifiers such as first and last name are collected, however, in both the ECR and the PHARMO RLS data are de-identified (i.e., all personal identifiers are removed from the file) and the researchers do not have direct access to identifiable information.

Patients are informed of the existence of the PHARMO RLS by leaflets and posters in the offices of the data suppliers. Each patient can object the use of his or her data for the PHARMO RLS. To opt-out, the patient informs the data supplier of his/her objection to the use of the data. The technical infrastructure of the PHARMO RLS allows individual data suppliers to withdraw data on the level of all data related to a certain patient, or specific data elements. If data are withdrawn, a message is sent to the PHARMO Institute, and the data will subsequently be removed from the PHARMO RLS. The CCCS considers the research performed with the ECR as being part of the process of quality assessment aimed to facilitate the attending physicians to deliver optimal cancer care. Such observational research is not considered 'experimental' for which informed consent should be obtained. The fact that caregivers receive aggregated feedback on the data they submitted does not change that.

The record linkage process (using indirectly identifiable patient information) of the ECR and the PHARMO RLS is executed in a separate department of the PHARMO Institute. The original patients variables used in the linking process will be kept separately from the data analysis files. After the linkage data is available for research in the PHARMO Research Database (PRD) where patients can be recognized by a PHARMO generated anonymized patient number linked to the anonymized ECR patient number. Variables that might allow for the re-identification, such as exact date of birth and zip code, have been removed or recoded. Only year of birth and gender of each patient is available in the research dataset.

After linkage, it is necessary that the privacy regulations of the CCCS and the PHARMO RLS are similar, because otherwise the confidentiality of the PHARMO RLS might be violated when accessing the ECR-PHARMO cohort via the ECR, or the other way around. As a result of the linkage, more specific event information of a single patient becomes available potentially leading to indirectly identifiability of the patient. Hence the ECR-PHARMO cohort should, next to the governance rules of the CCCS and the PHARMO RLS, also comply with a third, separate set of governance rules specifically of the ECR-PHARMO

cohort. In the future, further privacy protection of the data of the ECR-PHARMO cohort will be achieved by deleting certain datasets or by aggregating to a more general level and converting the records to files that do not contain original time stamped event of patients, but do allow observational research.

Research ethics

The use of the ECR-PHARMO cohort is controlled by an independent regional privacy committee, which consists of representatives of the participating data suppliers, patient representatives and an independent privacy expert. Every study requires permission of this committee. For each study, not only the research question, but also the data used for the study, the methods used to analyse the data, and the people/organisations who commissioned the study have to be described. All decisions of the privacy committee are based on the involved legislation in the Netherlands, e.g. the Personal Data Protection Act (Wet bescherming persoonsgegevens; Wbp)) and the Medical Treatment Contract Act (Wet Geneeskundige Behandelings Overeenkomst; WGBO). Within this legal framework, the Code of Conduct "Use of Data in Health Research"[40] is an important document for the interpretation of the use of this kind of data for scientific research in the Netherlands, and is approved by the Dutch Data Protection Authority (College Bescherming Persoonsgegevens; CBP). For the renewal of this approval, which expires every five years, a policy document on Trusted Third Parties (TTP) is currently being processed[41].

In some cases the privacy committee can advise review by a medical ethical committee. However, research projects that are based solely on registry data or existing medical records (i.e., without contact with the registered subjects) are exempt from review by an ethics committee provided that confidentiality and anonymity of patients is assured, as described above. These research projects are often discussed in tumour study groups, because the studies somehow reflect quality of care and therefore require involvement of the various specialists who are then made partly responsible for interpretation of the study results. Ethical review of a certified ethical committee is mandatory if the project entails any form of intervention, change in routine care or a direct contact with a patient, which has any impact on patients' mental integrity[42]. For example, when patients are to be enrolled in prospective studies (e.g. extensive questionnaire studies or studies that require additional tests or procedures which might hamper safety of patients) and re-identification of patients' information is needed, then the Dutch law mandates informed consent.

The governance rules of the CCCS and the PHARMO Institute as described above, also define whether third parties (researchers other than those from the CCCS or the PHARMO Institute) can have access to the data. First of all, data from the ECR-PHARMO cohort may under no circumstances be transferred for purposes other than scientific research. It is the responsibility of the investigator to consider the strengths and weaknesses in deciding

whether to use the linked ECR-PHARMO cohort for their research. A researcher must be trained and familiar with the data included in both databases and understand how the individual databases were generated, before using the data for research. This prevents inexperienced researchers to make decisions that might harm data providers or interfere with the common practice of care delivery. Investigators who wish to obtain data from the linked ECR-PHARMO cohort need to get permission from both the CCCS (where the relevant tumour study group will be consulted) and the PHARMO Institute, as technically they should respect the governance rules of both data providers. Contracts should be in place that enable control of the compliance of third parties with governance rules. Publications of results require the previous consent of both the CCCS and the PHARMO Institute. In this way, the continuity of access for other researchers to the ECR-PHARMO cohort is safeguarded.

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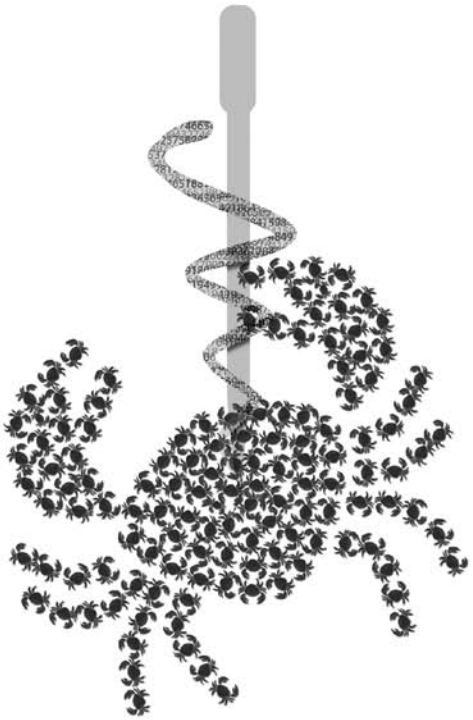
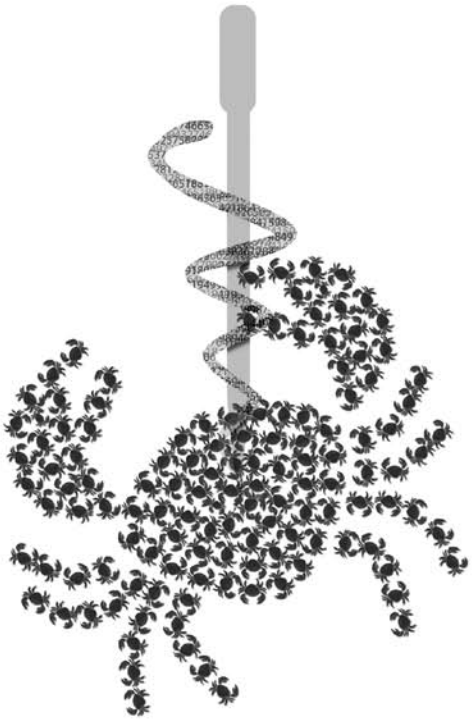
8.5 Concluding remarks



Concluding remarks

The ECR-PHARMO cohort created in this thesis is a valuable source available to researchers for pharmacoepidemiological studies in the area of oncology. It is particularly useful for epidemiologists dealing with outcomes involving effectiveness and safety of oncology drugs, especially with the new morbidities the new anti-cancer drugs may create.
The size of the cohort of approximately one million inhabitants is still relatively limited for studies in rare types of cancer; however, we demonstrated that pharmacoepidemiological studies in a cohort of breast cancer patients are feasible. This thesis only presented a few examples of such studies and many aspects of the pharmacoepidemiology in breast cancer patients still need to be addressed. Next to breast cancer, other common cancers types such as colorectal cancer, lung cancer and prostate cancer can also be studied using the current ECR-PHARMO cohort, including the research possibilities as described in the previous section.
The ECR-PHARMO cohort serves as a tool to raise hypotheses and provide population-based evidence that, added to evidence obtained from randomized controlled trials, would protect cancer patients from unnecessary risk while preserving treatment benefits. The ultimate goal of this cohort is to ensure that the pharmacologic aspects of cancer control becomes measurable and a subject of objective evaluation to support public health efforts. Its goal is to improve cancer surveillance, or, more specifically, to improve evaluation of cancer treatment outcome and safety of cancer patients.

Summary



Summary

The number of patients ever diagnosed with breast cancer in the Netherlands is growing considerably due to the increasing breast cancer incidence and the improving survival. Recent decades have brought a dramatic increase in the number of new agents being investigated and approved for the treatment of breast cancer. New drugs can increase the efficacy of breast cancer treatment, but may also generate late morbidities which may not be detectable in clinical trials.
This thesis describes the results of population-based observational studies on the use of systemic treatment (chemotherapy and endocrine therapy) in patients with breast cancer, as well as studies on morbidities that may occur after breast cancer diagnosis and treatment. Both the observed treatment and new morbidities may be different in everyday practice than expected from randomized clinical trials due to the heterogeneity of patients, their age, co-morbidity, co-medication and treatment compliance.
To be able to perform pharmacoepidemiological studies in a cohort of breast cancer patients in the Netherlands, a new data source was created by linking the Eindhoven Cancer Registry (ECR) and the PHARMO Record Linkage System (PHARMO RLS) as described in **Chapter 2.3**. The linked ECR-PHARMO cohort consists of 40,004 cancer patients newly diagnosed in the period 1998-2006, including 5,545 patients with breast cancer, 4,804 with colon and rectum cancer, 4,395 with lung cancer, and 3,835 with prostate cancer. The patient-centric data available from this linkage included, among other things, tumour information (histology, grade and stage) of incident cancers obtained from the ECR and data on drug treatment (out-patient and in-patient) and hospitalisations obtained from the PHARMO RLS, offering a longitudinal perspective.

The extent to which adjuvant systemic treatment patterns among women with early stage breast cancer have changed from 1990 through 2006 in the southeastern part of the Netherlands was assessed using data from solely the ECR (**Chapter 3**). The use of adjuvant systemic treatment for patients with breast cancer increased significantly over time, from 37% in 1990-1997, to 53% of all early stage breast cancer patients in 2002-2006. This increase was especially seen among patients with node-negative breast cancer. Marked variations were observed between hospitals, illustrating there have been early and late adopters of the treatment guidelines in the southeastern part of the Netherlands.
Not only more breast cancer patients received primary systemic treatment, there is also an increase in the number of drugs being approved for the treatment of patients with breast cancer. Data from the ECR breast cancer cohort linked with data from the PHARMO RLS allowed us to investigate trends in type of chemotherapy regimens administered to early stage or metastatic breast cancer patients (**Chapter 4**). Early stage breast cancer patients receiving chemotherapy in the adjuvant setting were in general treated according to the guidelines. For breast cancer patients who received palliative chemotherapy at diagnosis or after breast cancer recurrence, there was a large variation in chemotherapy regimens

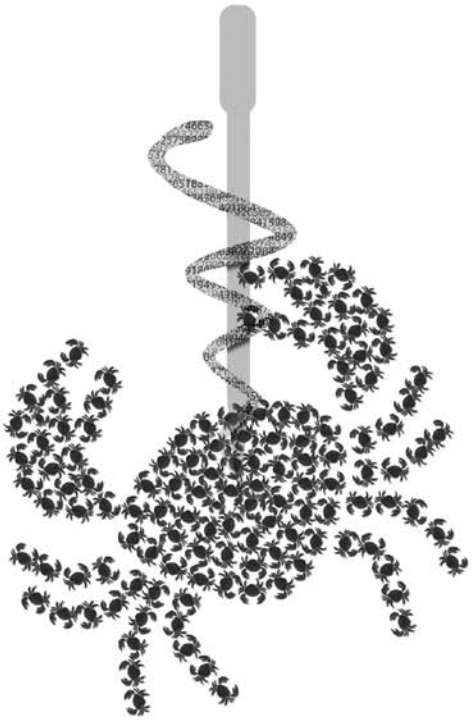
administered, which is probably due to the high variability in individual presentation. Presenting results on the administration of chemotherapeutics in everyday clinical practice is a way to give feedback to specialists as they are able to compare their practice patterns with the overall observed treatment patterns of breast cancer patients in the region.
Adjuvant endocrine treatment is recommended for women with hormone receptor-positive early stage breast cancer. The major concern in daily clinical practice is that patients should continue their endocrine treatment over the recommended period of five years. A population-based setting is needed to determine rates of discontinuation in daily practice as patients appear to discontinue their medications at higher rates in practice settings than in clinical trials. Data from the PHARMO community pharmacy database was used to determine the treatment pattern of endocrine therapy use of patients with breast cancer included in the ECR-PHARMO cohort (**Chapter 5**). This observational study showed that of patients with early stage breast cancer who started tamoxifen treatment, 49% continuously used endocrine treatment (tamoxifen and/or aromatase inhibitors) over a five year follow-up period. Older age (older than 70 versus 50-69 years) and two or more concomitant diseases (versus none) were independently associated with discontinuation of endocrine therapy. These results will assist the clinician to identify patients who are at increased risk of discontinuation of endocrine treatment, so that these patients can receive more intensive follow-up care to prevent early discontinuation.

Defining the incidence of new morbidities after breast cancer diagnosis and treatment becomes increasingly important as a growing number of breast cancer patients live cancer-free after diagnosis and treatment. In **Chapter 6** the incidence of cardiovascular morbidities were assessed among breast cancer patients included in the ECR-PHARMO cohort who had received chemotherapy. Incidence rates of cardiovascular morbidity were similar for breast cancer patients who underwent cardiotoxic or non-cardiotoxic chemotherapy during a median follow-up of 1.5 years. In this study, patients with pre-existing cardiovascular morbidity or older age were less likely to receive cardiotoxic chemotherapy. If specialists are aware of the cardiotoxicity of a certain chemotherapeutic, patients with breast cancer at risk for cardiovascular events will be less likely to receive such chemotherapeutics or adaptations will be made in dose and rate of administration.
In **Chapter 7** the occurrences of the more serious venous and arterial thromboembolic events were determined in patients with breast cancer by using hospitalisation data. This study showed that compared to cancer-free controls, breast cancer patients had a more than two times higher risk to have had a hospitalisation for myocardial infarction, ischaemic stroke and pulmonary embolism in the 12 months before breast cancer hospitalisation. This might be explained by the fact that breast cancer and thrombosis share similar risk factors such as obesity. Directly after breast cancer hospitalisation, patients experienced an extreme high risk of pulmonary embolism, which declined gradually during follow-up. Breast cancer treatment-related factors, such as the use of chemotherapy, hormonal therapy or duration of hospital stay were independent risk

factors for developing pulmonary embolism. To achieve optimal treatment and prognosis among patients diagnosed with breast cancer, this study contributes to the awareness of presence of thrombosis at breast cancer diagnosis and the incidence of thromboembolic morbidities after breast cancer diagnosis and treatment.

Next to the studies described in this thesis, the created ECR-PHARMO cohort facilitates many pharmacoepidemiology and outcomes research in various other cancer types. The uniqueness of the data available in the ECR-PHARMO cohort was addressed by comparing this linkage to other database linkages in Northern America and Europe (**Chapter 8.2**). Two exceptional features of the ECR-PHARMO cohort compared to the other linked databases are that the ECR is the only cancer registry that includes information on co-morbidity at diagnosis of cancer and the PHARMO RLS includes data on all (anti-cancer) drugs that have been dispensed by community pharmacies as well as in-hospital pharmacies. These data were not available in the other database linkages.
In the future perspective, the representativeness of the ECR-PHARMO cohort was considered as well as the current data limitations and possible ways to overcome these limitations in the future by, for example, expansion of the data collection. Moreover, an overview of the many other pharmacoepidemiological studies possible using the ECR-PHARMO cohort was provided. Examples are: studies on drug use and the risk of cancer, studies on potential drug–drug interactions between anti-cancer drugs and non anti-cancer drugs and studies on follow-up treatment of cancer patients after primary treatment. Finally, important aspects for continuation of this cohort in the future were discussed, including data confidentiality, governance and research ethics.
In conclusion, this thesis presents how patients with breast cancer are systemically treated in daily clinical practice, as well as the morbidities that are present and may occur after breast cancer diagnosis and treatment. For this, the ECR, the PHARMO RLS and the new created ECR-PHARMO cohort were used. The ECR-PHARMO cohort is a valuable source especially for epidemiologists and clinicians dealing with treatment patterns, effectiveness and safety of (new) oncology drugs.

Samenvatting



Samenvatting

Het aantal vrouwen waarbij ooit borstkanker is gediagnosticeerd neemt toe. Dit komt enerzijds door een stijging van het aantal nieuwe gevallen van borstkanker, anderzijds doordat de kans op overleven na diagnose is verbeterd. Deze hogere kans op overleven is onder meer te danken aan de introductie van nieuwe geneesmiddelen in de afgelopen decennia. Naast verbetering van de behandeling van borstkanker kunnen deze medicijnen op de langere termijn echter ook ziekten veroorzaken die niet, of beperkt, in klinisch onderzoek zijn waargenomen.
In dit proefschrift worden de resultaten besproken van observationele studies waarin de behandeling van borstkankerpatiënten met chemotherapie of hormoontherapie centraal staat. Daarnaast wordt het ontstaan van ernstige aandoeningen na borstkankerdiagnose en –behandeling onderzocht. Zowel de behandeling als ziekten na behandeling kunnen in de dagelijkse praktijk afwijken van wat er verwacht wordt op basis van klinisch vergelijkend onderzoek aangezien patiënten in de dagelijkse praktijk vaak ouder zijn, minder therapietrouw zijn en meer bijkomende ziekten hebben.
Om farmaco-epidemiologisch onderzoek bij kankerpatiënten mogelijk te maken is er een nieuwe Nederlandse onderzoeksdatabank gecreëerd. Hiervoor is de kankerregistratie van het Integraal Kankercentrum Zuid (IKZ; Eindhoven Cancer Registry: ECR) gekoppeld aan de databanken van het PHARMO Instituut (PHARMO Record Linkage System: PHARMO RLS), zoals beschreven in **Hoofdstuk 2.3**. Het gekoppelde IKZ-PHARMO cohort bestaat uit 40.004 kankerpatiënten, gediagnosticeerd in de periode 1998-2006. Het cohort bevat onder andere 5.545 patiënten met borstkanker, 4.804 met dikkedarmkanker, 4.395 met longkanker en 3.835 met prostaatkanker. Gedetailleerde tumorgegevens (stadium, histologie en gradering) van deze patiënten zijn beschikbaar via de kankerregistratie en longitudinale gegevens van onder andere de afgifte van geneesmiddelen en ziekenhuisopnames zijn beschikbaar via de PHARMO databanken.

Met behulp van de gegevens van de kankerregistratie van het IKZ werd in patiënten met operabel mammacarcinoom de toename van behandeling met chemotherapie en/of hormoontherapie bestudeerd in de periode 1990-2006 (**Hoofdstuk 3**). Het percentage patiënten met operabel mammacarcinoom dat met geneesmiddelen werd behandeld nam toe van 37% in 1990-1997, tot 53% in 2002-2006. Deze toename was vooral te zien bij borstkankerpatiënten zonder lymfekliermetastasen. De toediening van behandeling met chemotherapie en/of hormoontherapie varieerde tussen de ziekenhuizen mogelijk als gevolg van snelle en trage navolging van de richtlijnen.
Naast een toename van het aantal borstkankerpatiënten dat met geneesmiddelen wordt behandeld, stijgt ook het aantal beschikbare geneesmiddelen. Trends in de chemotherapieschema's verstrekt aan patiënten met een operabel of gemetastaseerd mammacarcinoom werden beschreven met behulp van de gegevens uit het IKZ-PHARMO cohort (**Hoofdstuk 4**). Patiënten met primair operabel mammacarcinoom

werden overwegend behandeld volgens de richtlijnen. Bij patiënten met gemetastaseerd mammacarcinoom werd een grote variatie waargenomen in de toegediende palliatieve chemotherapie. Dit hangt vermoedelijk samen met de grote diversiteit in patiënten met gemetastaseerd mammacarcinoom. Terugkoppeling van de resultaten van deze studie aan de specialisten in de regio geeft inzicht in de manier waarop zij, als groep, hun borstkankerpatiënten behandelen en draagt bij aan de discussie over de behandeling van deze patiënten.
Adjuvante hormoonbehandeling wordt aanbevolen voor vrouwen met hormonaal gevoelig mammacarcinoom. Het belangrijkste aandachtspunt in de dagelijkse praktijk is dat deze patiënten hun hormoonbehandeling moeten continueren over een periode van vijf jaar. In observationele studies kan worden nagegaan hoeveel procent van de patiënten dit ook daadwerkelijk doet, aangezien verwacht wordt dat dit percentage lager ligt dan bij patiënten die geïncludeerd zijn in klinische studies. In dit proefschrift werd het continueren van hormoonbehandeling door de borstkankerpatiënten uit het IKZ-PHARMO cohort bepaald met behulp van afleveringen van hormoonrecepten uit de PHARMO openbare apotheekdatabank (**Hoofdstuk 5**). Van de borstkankerpatiënten die met tamoxifen startten, continueerde 49% hun hormoonbehandeling (tamoxifen en/of een aromataseremmer) over een periode van 5 jaar. Patiënten ouder dan 70 jaar stopten vaker voortijdig de behandeling dan patiënten tussen 50 en 69 jaar. Hoe meer andere ziekten een patiënte had ten tijde van borstkankerdiagnose, hoe groter de kans was dat ze de hormoonbehandeling voortijdig zou staken. Als de behandelend arts zich ervan bewust is dat patiënten met deze kenmerken een verhoogd risico hebben op het voortijdig stoppen van hormoonbehandeling, dan kunnen deze patiënten intensiever gevolgd worden zodat dit voorkomen kan worden.

Onderzoek naar het ontstaan van nieuwe aandoeningen na borstkankerdiagnose en -behandeling wordt steeds belangrijker door het toenemende aantal borstkankerpatiënten dat na behandeling kankervrij is, of waarbij de borstkanker na behandeling onder controle is. In **Hoofdstuk 6** werd het optreden van hart- en vaatziekten na toediening van chemotherapie bestudeerd voor de borstkankerpatiënten uit het IKZ-PHARMO cohort. De incidentie van hart- en vaatziekten anderhalf jaar na chemotherapiebehandeling bleek niet verhoogd na toediening van cardiotoxische chemotherapeutica vergeleken met niet-cardiotoxische chemotherapeutica. Ouderen of patiënten met hart- en vaatziekten op het moment van diagnose kregen minder vaak cardiotoxische chemotherapeutica toegediend. Specialisten lijken rekening te houden met de aanwezigheid van hart- en vaatziekten bij de keuze van het soort chemotherapeutica, of verlagen de dosis van het geneesmiddel als het een cardiotoxisch chemotherapeutica betreft.
In **Hoofdstuk 7** werd bij patiënten met een ziekenhuisopname voor borstkanker het optreden van een ziekenhuisopname voor trombose bepaald met behulp van gegevens uit de PHARMO databanken. Borstkankerpatiënten bleken in het jaar voor diagnose een meer dan twee keer verhoogde kans te hebben op een ziekenhuisopname voor een hartinfarct,

herseninfarct en longembolie in vergelijking met patiënten zonder kanker. Mogelijk is dit te verklaren doordat factoren zoals overgewicht het risico op zowel borstkanker als trombose verhogen. Direct na ziekenhuisopname voor borstkanker hadden patiënten een sterk verhoogd risico op het krijgen van een longembolie. Dat risico daalde naarmate de ziekenhuisopname voor borstkanker langer geleden was. Borstkankerbehandeling en factoren die een verband hebben met de behandeling, zoals duur van ziekenhuisopname, verhogen de kans op het krijgen van een longembolie. Deze studie draagt bij aan de bewustwording van de aanwezigheid van trombose in borstkankerpatiënten en het risico op het ontstaan van trombose na behandeling van patiënten met borstkanker.

Naast de studies beschreven in dit proefschrift, geeft de IKZ-PHARMO koppeling de mogelijkheid om farmaco-epidemiologisch onderzoek en uitkomstenonderzoek te doen in veel andere kankersoorten, mits de patiëntenaantallen dit toestaan. Om de bijzondere positie van het IKZ-PHARMO cohort in kaart te brengen werd deze koppeling vergeleken met soortgelijke registratiekoppelingen uit Noord-Amerika en Europa (**Hoofdstuk 8.2**). In vergelijking met de andere databronnen bleek het IKZ-PHARMO cohort bijzonder op twee aspecten: de aanwezigheid van comorbiditeit ten tijde van kankerdiagnose zoals geregistreerd in de kankerregistratie van het IKZ en de gegevens over de toediening van alle (anti-kanker)geneesmiddelen (zowel intra- als extramuraal) beschikbaar via de PHARMO databanken. Deze data waren niet aanwezig in de andere registratiekoppelingen.
Dit proefschrift eindigt met een beschrijving van de representativititeit van het IKZ-PHARMO cohort, de huidige beperkingen van de beschikbare gegevens en de mogelijkheden tot verbetering en uitbreiding van de datacollecties. Ook wordt er een overzicht gegeven van farmaco-epidemiologische studies, die naast de studies beschreven in dit proefschrift, uitgevoerd zouden kunnen worden met de gegevens van het IKZ-PHARMO cohort. Voorbeelden zijn: onderzoek naar geneesmiddelengebruik en het risico op kanker, onderzoek naar geneesmiddeleninteracties tussen kankermedicijnen en andere medicijnen en onderzoek naar vervolgbehandeling van kankerpatiënten na primaire behandeling. Daarnaast worden aspecten belangrijk voor de continuïteit van het IKZ-PHARMO cohort beschreven, zoals regelgeving, privacy en veiligheid rondom het gebruik van de data.
Concluderend kan gesteld worden dat dit proefschrift inzicht geeft in het gebruik van geneesmiddelen door borstkankerpatiënten in de dagelijkse praktijk en het ontstaan van andere ernstige aandoeningen na borstkankerdiagnose en -behandeling. Deze resultaten zijn verkregen met behulp van de van de kankerregistratie van het IKZ, de databanken van het PHARMO Instituut en het gekoppelde IKZ-PHARMO cohort. Dit IKZ-PHARMO cohort biedt nieuwe mogelijkheden voor epidemiologen en clinici die onderzoek doen naar het gebruik, de effectiviteit en veiligheid van (nieuwe) geneesmiddelen voor de behandeling van kanker.

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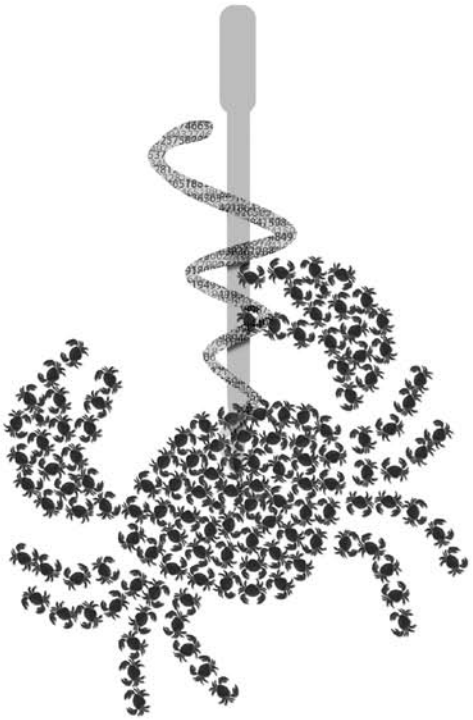

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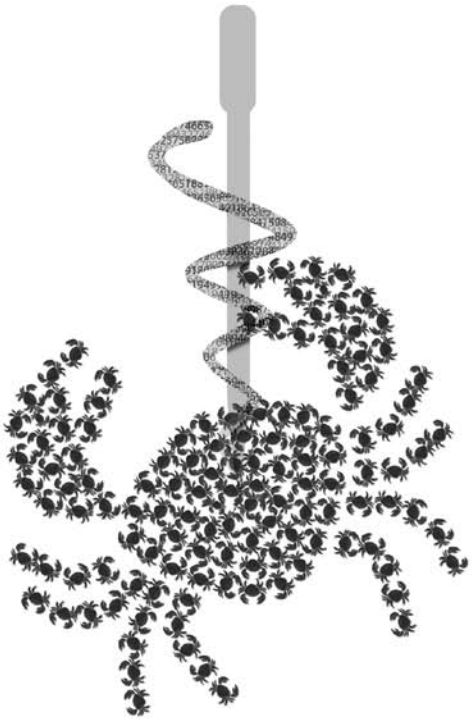
Gerard (Art) Vreugdenhil, MD, PhD
Department of Internal Medicine, Máxima Medical Centre, Veldhoven, The Netherlands

List of publications



Publications in this thesis

1. **van Herk-Sukel MP**, van de Poll-Franse LV, Lemmens VE, Vreugdenhil G, Pruijt JF, Coebergh JW, Herings RM. New opportunities for drug outcomes research in cancer patients: the linkage of the Eindhoven Cancer Registry and the PHARMO Record Linkage System. ***Eur J Cancer*** 2010;46:395-404.

2. **Sukel MP**, van de Poll-Franse LV, Nieuwenhuijzen GA, Vreugdenhil G, Herings RM, Coebergh JW, Voogd AC. Substantial increase in the use of adjuvant systemic treatment for early stage breast cancer reflects changes in guidelines in the period 1990-2006 in the southeastern Netherlands. ***Eur J Cancer*** 2008;44:1846-54.

3. **van Herk-Sukel MP**, van de Poll-Franse LV, Creemers GJ, Lemmens VE, van der Linden PD, Herings RM, Coebergh JW, Voogd AC. Major changes in chemotherapy regimens administered to breast cancer patients during 2000-2008. ***Submitted***.

4. **van Herk-Sukel MP**, van de Poll-Franse LV, Voogd AC, Nieuwenhuijzen GA, Coebergh JW, Herings RM. Half of breast cancer patients discontinue tamoxifen and any endocrine treatment before the end of the recommended treatment period of 5 years: a population-based analysis. ***Breast Cancer Res Treat*** 2010;122:843-51.

5. **Sukel MP**, Breekveldt-Postma NS, Erkens JA, van der Linden PD, Beiderbeck AB, Coebergh JW, Herings RM. Incidence of cardiovascular events in breast cancer patients receiving chemotherapy in clinical practice. ***Pharmacoepidemiol Drug Saf*** 2008;17:125-34.

6. **van Herk-Sukel MP**, Shantakumar S, Kamphuisen PW, Penning-van Beest FJ, Herings RM. Myocardial infarction, ischaemic stroke and pulmonary embolism before and after breast cancer hospitalization: a population-based study. ***Thrombosis and Haemostasis*** 2011;106:149-55

7. **van Herk-Sukel MP**, Lemmens VE, van de Poll-Franse LV, Herings RM, Coebergh JW. Record linkage for pharmacoepidemiological studies in cancer patients. ***Pharmacoepidemiol Drug Saf*** 2011, in press.

Other publications

8. Goettsch WG, **Sukel MP**, van der Peet DL, van Riemsdijk MM, Herings RM. In-hospital use of opioids increases rate of coded postoperative paralytic ileus. *Pharmacoepidemiol Drug Saf* 2007;16:668-74.

9. **Sukel MP**, van der Linden MW, Chen C, Erkens JA, Herings RM. Large-scale stopping and switching treatment with COX-2 inhibitors after the rofecoxib withdrawal. *Pharmacoepidemiol Drug Saf* 2008;17:9-19.

10. van der Linden MW, Gaugris S, Kuipers EJ, **van Herk-Sukel MP**, van den Bemt BJ, Sen SS, Herings RM. COX-2 inhibitors: complex association with lower risk of hospitalization for gastrointestinal events compared to traditional NSAIDs plus proton pump inhibitors. *Pharmacoepidemiol Drug Saf* 2009;18:880-90.

11. van der Linden MW, Gaugris S, Kuipers EJ, van den Bemt BJ, **van Herk-Sukel MP**, Herings RM. Gastroprotection among new chronic users of non-steroidal anti-inflammatory drugs: a study of utilization and adherence in The Netherlands. *Curr Med Res Opin* 2009;25:195-204.

12. Dezentje VO, van Blijderveen NJ, Gelderblom H, Putter H, **van Herk-Sukel MP**, Casparie MK, Egberts AC, Nortier JW, Guchelaar HJ. Effect of concomitant CYP2D6 inhibitor use and tamoxifen adherence on breast cancer recurrence in early-stage breast cancer. *J Clin Oncol* 2010;28:2423-9.

13. Dezentje VO, van Blijderveen NJ, Gelderblom H, Putter H, **van Herk-Sukel MP**, Casparie MK, Egberts AC, Nortier JW, Guchelaar HJ. Reply to R. Ferraldeschi et al. *J Clin Oncol* 2010;28:e586.

14. Penning-van Beest FJ, **van Herk-Sukel MP**, Gale R, Lammers JW, Herings RM. Three-year dispensing patterns with long-acting inhaled drugs in COPD: a database analysis. *Respir Med* 2010;105:259-65.

15. Landis SH, El-Hariry IA, **van Herk-Sukel MP**, van den Haak P, Janssen-Heijnen ML, Penning-van Beest FJ, Herings RM. Prevalence and incidence of acute and chronic co-morbidity in patients with squamous cell carcinoma of the head and neck. *Head & Neck* 2011, in press.

16. Timmers L, Beckeringh JJ, **van Herk-Sukel MP**, Bovend E, Hugtenburg JG. Use and costs of oral anti-cancer agents in the Netherlands in the period 2000- 2008. *Pharmacoepidemiol Drug Saf* 2011, in press.

17. Overbeek JA, Zhao Z, **van Herk-Sukel MP**, Barber BL, Gao S, Herings RM. Costs of hospital events in patients with metastatic colorectal cancer. *J Med Econ* 2011, in press.

18. Ruiter R, Visser LE, **van Herk-Sukel MP**, Coebergh JW, Haak HR, Geelhoed-Duijvestijn PH, Straus SM, Herings RM, Stricker BH. Risk of cancer in patients on insulin glargine and other insulin analogues in comparison to those on human insulin: results from a large population-based follow-up study. *Diabetologia* 2011, in press

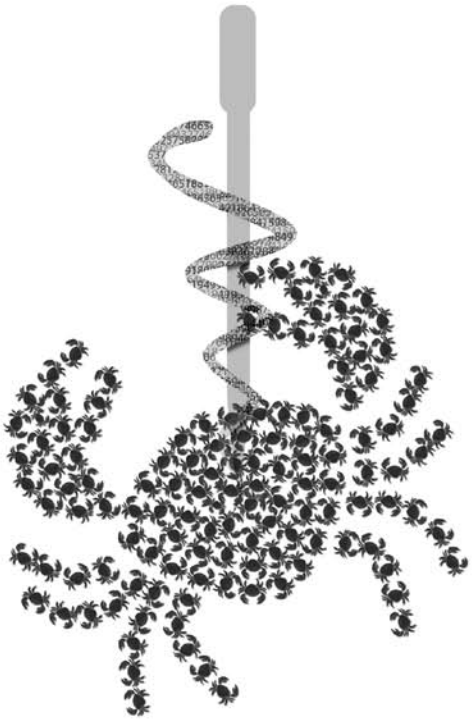
19. Overbeek JA, Zhao Z, **van Herk-Sukel MP**, Barber BL, Gao S, Herings RM. Cardiovascular co-morbidities among patients with metastatic colorectal cancer. *Submitted*.

20. Ruiter R, Visser LE, **van Herk-Sukel MP**, Geelhoed-Duijvestijn PH, de Bie S, Straus SM, Mol PG, Romio SA, Herings RM, Stricker BH. Trends in dispensing patterns of rosiglitazone and pioglitazone in the Netherlands following safety signals during the period 1998–2008. *Submitted*.

21. Ruiter R, Visser LE, **van Herk-Sukel MP**, Coebergh JW, Haak HR, Geelhoed-Duijvestijn PH, Straus SM, Herings RM, Stricker BH. Risk of cancer in patients on metformin in comparison to those on sulfonylurea derivatives: results from a large population–based follow-up study. *Submitted*.

22. Bastiaannet E, Sampieri K, Dekkers OM, de Craen AJ, **van Herk-Sukel MP**, Lemmens VE, van den Broek CB, Coebergh JW, Herings RM, van de Velde CJ, Fodde R, Liefers GJ. Use of Aspirin postdiagnosis improves survival for colon cancer patients. ***Submitted***.

Dankwoord



Dankwoord

In tegenstelling tot de aftiteling van een speelfilm, waar meestal weinig interesse voor is, is het dankwoord één van de meest gelezen onderdelen van het proefschrift. Ik vind het belangrijk om de mensen die mij tijdens mijn promotietraject hebben bijgestaan te bedanken, want hoewel mijn naam op de voorkant van dit proefschrift staat, is dit niet het resultaat van één persoon. Om de vergelijking met de speelfilm aan te houden: deze kan niet bestaan zonder regisseur, script, decor en spelers. Ik houd de aftiteling van dit proefschrift kort en bondig, aangezien ik graag iedereen verder persoonlijk bedank. Hieronder noem ik de mensen die mij tijdens mijn promotietraject hebben bijgestaan, geadviseerd, geïnspireerd en gemotiveerd.

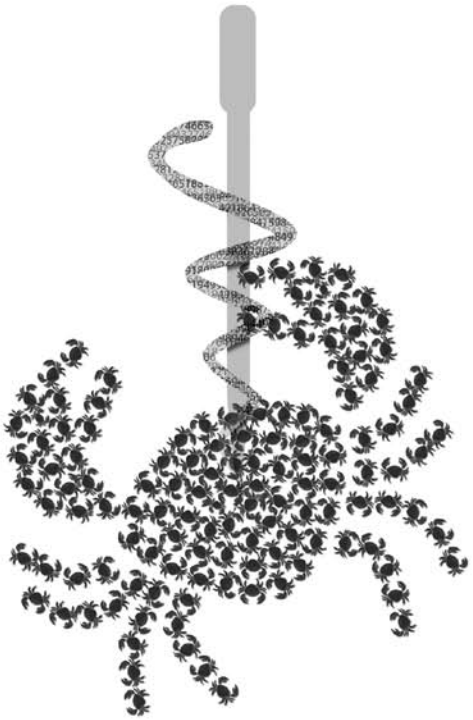
Allereerst mijn promotor, Jan Willem, en mijn copromotoren, Ron en Lonneke. Zonder jullie was de promotie überhaupt nooit een feit geweest. Ik dank jullie, naast de inhoudelijke ondersteuning, voor de belangrijke levenslessen en de gezelligheid tijdens de besprekingen van het onderzoek.

De beoordeling van het script door de leden van de kleine commissie en daarnaast de overige leden van de promotiecommissie: veel dank voor de bereidheid mijn proefschrift te lezen en ik zie uit naar de gedachtewisseling over de inhoud van dit proefschrift.

Het decor van mijn promotie was het PHARMO Instituut, met als directeur Ernst, die mij de ruimte heeft gegeven om naast mijn onderzoeksbaan ook een promotietraject te volgen. Ik waardeer de samenwerking met mijn medespelers, de (ex-)collega's van het PHARMO instituut. Jullie zorgen ervoor dat ik met veel plezier en enthousiasme naar mijn werk ga. Hierbij wil ik vooral noemen mijn kamergenote Fernie en natuurlijk ook Jetty en Leanne: bedankt dat jullie naast mij willen staan tijdens de verdediging! Ook de clinici, collega-epidemiologen, Valery en de andere onderzoekers van het IKZ met wie ik heb samengewerkt tijdens het schrijven van de artikelen wil ik bedanken, ik verheug me op de volgende projecten die van start gaan.

Naast het werk zorgt mijn privéleven voor juiste balans en heerlijke relativering. Lieve zussen, (schoon)familie en vrienden, velen van jullie hebben geen idee wat voor werk ik inhoudelijk doe, maar dat hoeft ook niet, want naast mijn werk zijn er zoveel andere zaken om van te genieten samen met jullie. Lieve papa en mama, bedankt voor jullie onvoorwaardelijke liefde en steun. Lieve Herman, wat ben ik iedere dag weer blij en gelukkig dat jij en Mads in mijn leven zijn.

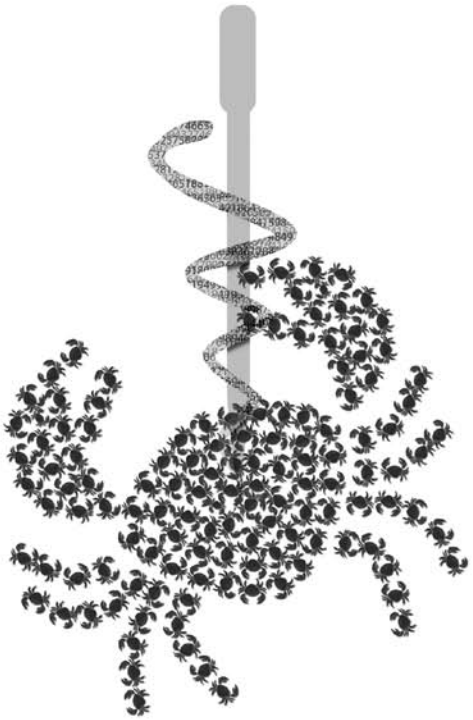
Curriculum Vitae



Curriculum Vitae

Myrthe Pieternella Paulina Sukel werd geboren in Etten-Leur op 22 november 1980. In 1999 behaalde zij haar VWO diploma aan de Katholieke Scholengemeenschap Etten-Leur waarna zij begon met haar studie Voeding en Gezondheid aan de Wageningen Universiteit. Tijdens haar afstudeervak bij Numico Research B.V. deed ze onderzoek naar de variatie in darmpermeabiliteit bij gezonde vrijwilligers. Aan de Griffith University (Gold Coast, Australië) doorliep zij haar stage bij de Nutrition Unit waar ze onderzoek deed naar de betrokkenheid van diëtisten in voedingsonderzoek. Voor haar tweede afstudeervak bij het Universitair Medisch Centrum Utrecht deed ze onderzoek naar het effect van immunonutritie op de ontlasting bij IC-patiënten die een hart- of longoperatie hadden ondergaan. In maart 2004 studeerde zij cum laude af, met als specialisatie Voedingsleer.
Sinds april 2004 is Myrthe werkzaam bij het PHARMO Instituut. Zij is gestart als junior onderzoeker met als hoofdwerkzaamheden de uitvoering van farmaco-epidemiologisch onderzoek binnen verschillende ziektegebieden. Vervolgens was zij in de periode 2006-2008 werkzaam als onderzoeker, waarvan een half jaar als business development manager waarbij het contact met opdrachtgevers en het ontwikkelen van onderzoeksprotocollen centraal stond. Sinds 2008 is zij werkzaam als senioronderzoeker met als aandachtsgebied oncologie en sinds 2009 is zij geregistreerd als epidemioloog A. Ze werkte mee aan het tot stand komen van de koppelingen van de PHARMO databanken met externe registraties op het gebied van de oncologie: de PALGA (Pathologisch Anatomisch Landelijk Geautomatiseerd Archief) en het IKZ (Integraal Kankercentrum Zuid), en is vanuit het PHARMO instituut de projectleider van de farmaco-epidemiologische onderzoeken op het gebied van kanker. Voortvloeiend uit de gemaakte IKZ-PHARMO koppeling verrichtte zij sinds 2006 onderzoek naar het gebruik van geneesmiddelen bij patiënten met borstkanker. De beschrijving van de koppeling en de bundeling van de borstkankerstudies heeft geresulteerd in dit proefschrift.
In oktober 2008 trouwde zij met Herman van Herk en sinds april 2010 hebben zij samen een zoon Mads.

PhD portfolio summary



Summary of PhD training and teaching activities

Name PhD student:	Myrthe van Herk-Sukel
Erasmus MC Department:	Public Health/ PHARMO Intitute for Drug Outcomes Research
Research School:	o.a. NIHES
PhD period:	2006- 2011
Promotor:	Prof. Dr. Jan Willem W. Coebergh
Supervisors:	Dr. R.M.C. Herings / Dr. L.V. van de Poll-Franse

1. PhD training

	Year	Workload (Hours/ECTS)
General academic skills		
- Biomedical English Writing and Communication	2006-2011	40 hrs (1.4 ECTS)
- Research Integrity	2006-2011	40 hrs (1.4 ECTS)
Research skills		
- Statistics	2006-2011	40 hrs (1.4 ECTS)
- Methodology	2006-2011	40 hrs (1.4 ECTS)
- 'Principles of Epidemiologic Data Analysis', Netherlands Institute for Health Sciences (NIHES)	2006	40 hrs (1.4 ECTS)
In-depth courses (e.g. Research school, Medical Training)		
- 'Cancer Epidemiology', NIHES	2006	40 hrs (1.4 ECTS)
- 'Farmacotherapie colleges', Netherlands Centre for Post-Academic Education in Pharmaceutical Sciences	2006	64 hrs (2.3 ECTS)
- 'Basiscursus oncologie', Nederlandse Vereniging voor Oncologie	2007	40 hrs (1.4 ECTS)

Presentations

- Poster presentation at International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE)	2006	32 hrs (1.1 ECTS)
- Oral presentation at Integraal Kankercentrum Zuid (IKZ) breast cancer seminar	2007	32 hrs (1.1 ECTS)
- Poster presentation at 6th European Breast Cancer Conference (EBCC6)	2008	32 hrs (1.1 ECTS)
- Poster presentation at International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	2008	32 hrs (1.1 ECTS)
- Oral presentation at Breast Cancer Symposium, 'Nieuwe Ontwikkelingen bij de Behandeling van het Mammacarcinoom'	2009	32 hrs (1.1 ECTS)
- Oral presentation at IKZ medical oncology seminar	2009	32 hrs (1.1 ECTS)
- Oral and poster presentation at ICPE	2009	64 hrs (2.3 ECTS)
- Poster presentation at joint 15th Congress of the European CanCer Organisation and 34th Congress of the European Society for Medical Oncology (ECCO 15 and 34th ESMO)	2009	32 hrs (1.1 ECTS)
- Poster presentation at ISPOR	2009	32 hrs (1.1 ECTS)
- Poster presentation at 32nd Annual San Antonio Breast Cancer Symposium (SABCS)	2009	32 hrs (1.1 ECTS)
- Poster presentation at ISPOR	2010	32 hrs (1.1 ECTS)
- Oral presentation at "Leren door registreren", 55 jaar regionale kankerregistratie	2011	32 hrs (1.1 ECTS)
- Two poster presentations at ISPOR	2011	64 hrs (2.3 ECTS)
- Two poster presentations at ICPE	2011	64 hrs (2.3 ECTS)
- Five oral presentations at PHARMO seminars	2006-2011	160 hrs (5.7 ECTS)

International conferences

- United Kingdom Association of Cancer Registries (UKACR) and Netherlands Cancer Registry (NCR) Conference	2006	24 hrs (0.9 ECTS)
- ISPOR 9th Annual European Congress	2006	24 hrs (0.9 ECTS)
- ISPOR 12th Annual International Meeting	2007	24 hrs (0.9 ECTS)
- 6th European Breast Cancer Conference (EBCC6)	2008	32 hrs (1.1 ECTS)
- 25th Anniversary International Conference on Pharmacoepidemiology & Therapeutic Risk Management	2009	24 hrs (0.9 ECTS)

Dutch conferences		
- FIGON Dutch Medicines Days	2006	24 hrs (0.9 ECTS)
- Therapie op maat, 2de interdisciplinaire congres van de NVCO, NVMO en NVRO	2007	16 hrs (0.6 ECTS)
- Symposium 'Nieuwe Ontwikkelingen bij de Behandeling van het Mammacarcinoom'	2009	8 hrs (0.3 ECTS)
- NVvO-Oncologiedag Borstkanker	2011	8 hrs (0.3 ECTS)
2. Teaching activities		
	Year	**Workload (Hours/ECTS)**
Supervising Bachelor's theses		
- 'Literature review on cardiotoxicity and cancer', J. Kerkvliet, Department of Pharmaceutical Sciences, Utrecht University	2006	40 hrs (1.4 ECTS)
- 'Voorschrijfgedrag van cytostatica voor colorectaalkanker in zes Nederlandse ziekenhuizen', C. Verkroost, Department of Pharmaceutical Sciences, Utrecht University	2010	40 hrs (1.4 ECTS)
Supervising Master's theses		
- 'Overview of databases utilized in published literature for cancer surveillance', F.Bergsma, Department of Pharmaceutical Sciences, Utrecht University	2007	40 hrs (1.4 ECTS)
- 'NSAID exposure and risk of cancer', L.M. Hollestein, Master of Science in Clinical Epidemiology, NIHES	2011	40 hrs (1.4 ECTS)
TOTAL		**1,392 hrs (50 ECTS)**

The crab is the symbol for cancer and the pink colour represents breast cancer awareness. The crab is composed of many smaller crabs referring to the complexity of cancer and its treatment. The medicines used to treat breast cancer are symbolised by the pipette and snake; the symbol of medicine. The numbers and figures stand for the large, population-based data sources used for this research.