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Risk and prognosis of breast cancer among women at high risk of the disease

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“Don’t let the bird shit in your eye”- Grandma Kate, 95 years old

TO METTE, OLIVIA, MARCUS AND ERIK

Abstract
The overall objectives of this thesis were to increase our understanding of the risk and prognosis of breast cancer using the high risk groups of women with bilateral and familial breast cancer.
Data from the Swedish Cancer Register, the Multi-Generation Register and the Cause of Death register was used in Paper I-III to identify women with bilateral cancer and study risk and prognosis of the disease. The incidence of synchronous breast cancer (< 3 months of first cancer) increased by age and by 40% during the 1970s, whilst the incidence of metachronous cancer (≥ 3months of first cancer) decreased by age and by about 30% since the early 1980s most likely due to increasing use of adjuvant therapy. In the first 20 years following a diagnosis of primary breast cancer, the incidence of metachronous cancer decreased from about 0.8% to 0.4%/yr in patients diagnosed with the first breast cancer before age 45 years, whilst the incidence remained stable at 0.5–0.6%/yr among those who were older than 45 years at diagnosis. After 30 years of follow-up, the cumulative risk of metachronous bilateral breast cancer approached 15% regardless of age at first primary breast cancer. Women who developed bilateral cancer within 5 years and before age 50 were 3.9 times (95% CI 3.5-4.5) more likely to die from breast cancer than women with unilateral cancer. Women with a bilateral cancer diagnosed more than 10 years after the first cancer had a prognosis similar to that of a unilateral breast cancer. Adjuvant chemotherapy of primary cancer is a predictor of poor survival after diagnosis of early metachronous cancers.
In paper III we compared the incidence patterns of familial and non-familial bilateral disease to the risk of breast cancer in twin sisters identified using the Twin Registers of Sweden, Finland and Denmark. We observed differences in risk of breast cancer that are up to 5 to 7-fold larger in absolute terms with an entirely different age pattern when comparing the risk of disease in the opposite breast and in twin sisters to the general female population. The risk of cancer in the non-affected twin and the opposite breast was not affected by age or time since first event. The relative risk of familial bilateral cancer was 52% higher (IRR 1.52, 95%CI; 1.42-1.63) and the relative risk in the dizygotic twin sister was 26% lower (IRR 0.74 95%CI; 0.61-0.90) compared to the risk of non-familial bilateral cancer. In paper IV we assessed if breast cancer prognosis is inherited using a linked data set from the Swedish Cancer Register and the Multi-Generation register. We identified 3,618 mother-daughter and sister pairs with breast cancer and classified 5-year breast cancer specific prognosis among proband (mother or oldest sister) into tertiles as poor, intermediary or good. After adjusting for potential confounders daughters and sisters of a proband with poor prognosis had a 60 percent higher 5-year breast cancer mortality compared a proband with good prognosis (relative risk 1.6; 95%CI 1.2-2.2; p for trend 0.002).
In conclusion, the risk of familial disease is high and differs by age from the risk in the general population. The risk of bilateral breast cancer is high and prognosis is poor and both related to adjuvant therapy. Finally there is evidence that breast cancer prognosis is inherited.
Key words: Epidemiology, breast cancer, bilateral, familial, incidence, prognosis, age, latency, calendar period, adjuvant therapy

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List of papers

The thesis is based on the following papers:

1 Mikael Hartman, Kamila Czene, Marie Reilly, Jonas Bergh, Pagona Lagiou, Dimitrios Trichopoulos, Hans-Olov Adami, Per Hall.
Genetic implications of bilateral breast cancer: population based cohort study.
Lancet Oncol 2005;6(6):377-82.

2 Mikael Hartman, Kamila Czene, Marie Reilly, Jan Adolfsson, Jonas Bergh, Hans-Olov Adami, Paul W. Dickman, Per Hall.
Incidence and prognosis of synchronous and metachronous bilateral breast cancer.
Accepted *Journal of Clinical Oncology, 2007*

3 Mikael Hartman, Per Hall, Gustav Edgren, Marie Reilly, Paul Lichtenstein, Jaakko Kaprio, Axel Skytthe, Julian Peto, Kamila Czene.
Breast cancer onset in twins and in women with bilateral disease
Submitted

4 Mikael Hartman, Linda Lindström, Paul W. Dickman, Hans-Olov Adami, Per Hall, Kamila Czene.
Is breast cancer prognosis inherited?
Breast Cancer Research, 2007;9(3):R39

Abbreviations

CI	Confidence interval
HR	Hazard ratio
HRT	Hormone replacement therapy
ICD	International classification of disease
IRR	Incidence rate ratio
MRR	Mortality rate ratio
SIR	Standardized incidence rate

Introduction

Breast cancer, the most common cancer in women in the western world, has been associated with a number of risk factors including genetic alterations. Globally, increasing breast cancer incidence rates, improved prognosis and growing life expectancy have resulted in increasing number of women at risk of developing a bilateral primary breast cancer (1). In Sweden, the increase of breast cancer incidence is likely to be partly attributable to the introduction of mammography screening in the 1980´s and the widespread use of postmenopausal hormone replacement therapy (HRT) (2, 3), while the improvement in prognosis is probably attributed to both improved detection and treatment.

Despite a fairly good prognosis, approximately 30% of the women die from the disease, the health impact is substantial given the high incidence of breast cancer (4). The total body of research within the field of breast cancer is overwhelming, despite this fact there is limited information on the etiology and prognosis of the disease.

There are several methodological decisions that have to be made in order to study risk and prognosis effectively. We argue that a sensible approach is to identify groups of women with very high risk and also poor prognosis to increase our understanding of the disease. Two study populations that fulfill these criteria are women that develop two primary breast cancers, ie bilateral breast cancer and women with a family history of the disease. They both posses an increased risk of the disease and bilateral breast cancer has reportedly a very poor prognosis (5-7). There are to date several studies assessing the risk of familial cancer including breast cancer with relative risk estimates ranging from 1.6 to 4.3 when only a parent was affected and up to 8.5 when only a sibling was effected (8, 9). There is to our knowledge yet no one who has tested if not only risk but also prognosis might be inherited. In studies of both risk factors and prognosticators either of two approaches are normally used, randomized clinical trails and observational studies. Randomized clinical trials are of course preferable, but at the same time both costly, time consuming and sometimes very difficult to perform due to their prospective character. This leaves observational studies as the most common choice. Sweden provides readily available large cohorts of women with breast cancer from which subcohorts of women with familial and bilateral cancers can be identified and it was therefore our obvious choice. In summary, we set out to conduct 4 register based cohort studies assessing the risk and prognosis of bilateral and familial breast cancer in Sweden.

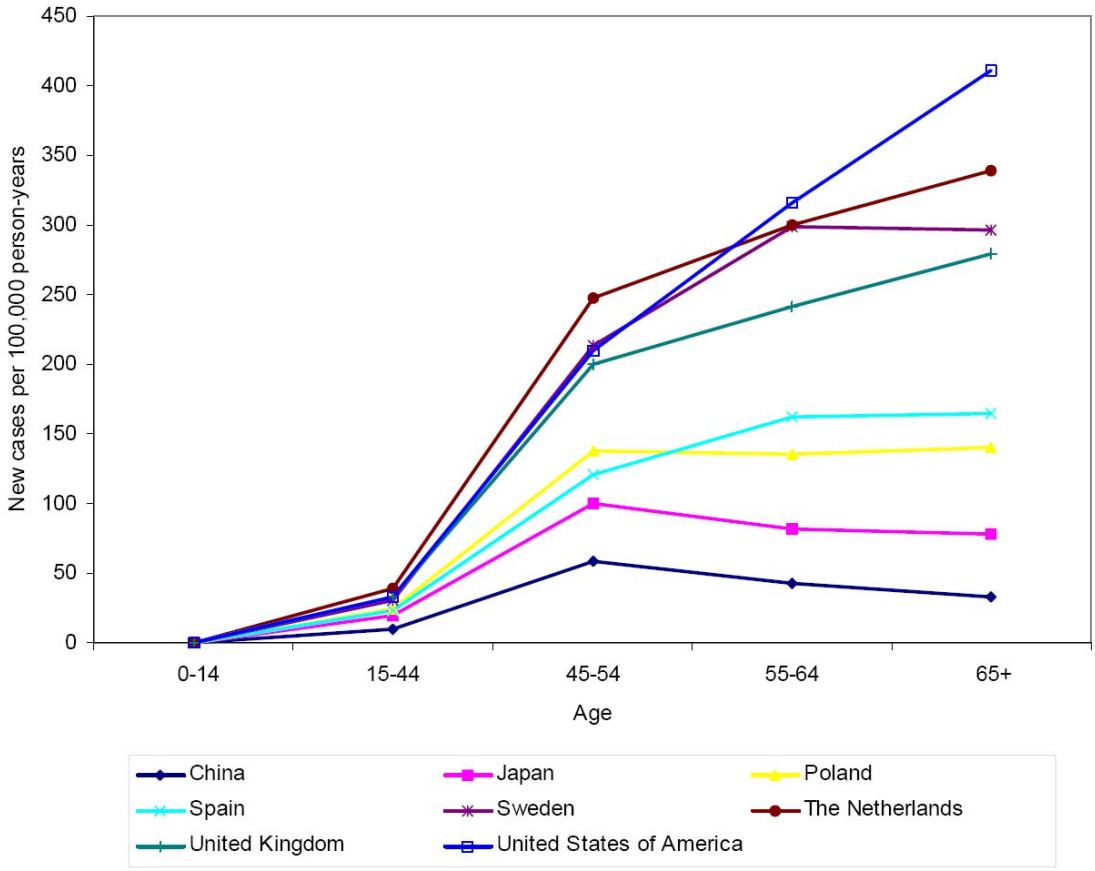
Background

Risk of breast cancer

Unilateral breast cancer

Breast cancer is the most common female malignancy world wide (10). Large differences in incidence between countries are seen, where women in wealthy westernized countries experience the highest risk (Figure 1). In Sweden approximately one woman in eight will develop the disease during her lifetime (2).

Figure 1. Age specific incidence rate of breast cancer per 100,000 person years. Adated from Ferlay et al, 2001

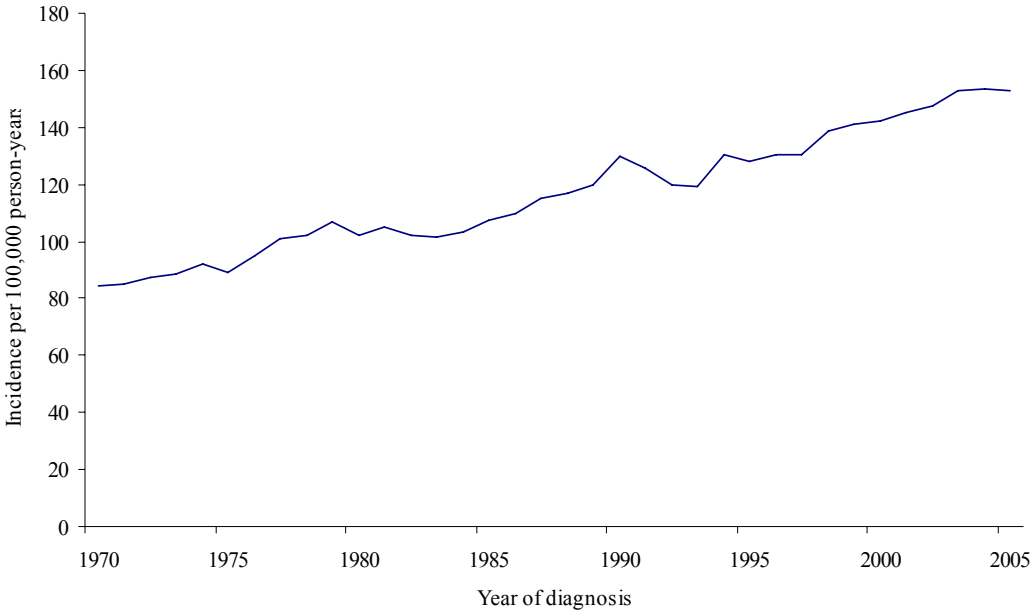


To date, several risk factors for breast cancer have been identified, the majority having direct or indirect association with female hormonal status. Reproductive factors such as number of children, age at first birth, duration of breast-feeding and the use of oral contraceptives and hormone replacement therapy have been demonstrated to affect the risk of breast cancer (11-14). The association of breast cancer with a number of other factors including height, alcohol consumption, smoking and nutrition, is still debated (15-18). High penetrant genes as well as common genetic variation has during recent years also been shown to have an association to the disease (19-24).

It has long been known that increasing age is associated with increased risk of breast cancer, but this is mostly true in westernized countries (Figure 1). Before the age of 45 years there are, on the absolute scale, very small differences in risk, while at increasing age the difference becomes close to 10-fold between women in countries like China and the United States of America. These differences can not be explained by variations in genetic risk since it is at increasing age we see the biggest differences (25). Rather it is more likely that lifestyle factors contribute to these variations in risk of disease. Furthermore age can be viewed as a proxy for the hormonal status of a woman, where at a premenopausal age (<45 years) she is under a constant influence of reproductive hormones while at an older age the cyclical cascade of reproductive hormones is turned off. The causes for the change in incidence rate around the age of menopause are not known, but there are suggestions that the hormonal milieu of the woman is involved (26).

In Sweden there are reliable cancer statistics since 1958 (2). Breast cancer incidence has since the start of the register been on a continuous increase (Figure 2). As mentioned previously, this increase has been partly attributed to the introduction of mammography screening in the 1980´s and the widespread use of HRT (2, 3). Although, none of these factors explain the increase in incidence prior to 1980, since the increase was just as obvious from the start of the register 1958. Other factors such as decreasing age at menarche, fertility patterns and other lifestyle factors must also be taken into consideration (26-29).

Figure 2. Incidence of female breast cancer in Sweden. Data from the Swedish Cancer Register



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Bilateral breast cancer

Bilateral breast cancer is the occurrence of two primary invasive tumors, one in each breast. It was identified as a clinical entity relatively late compared to many other malignancies (6, 30). In the literature, some studies consider only second primary malignancies that are diagnosed more than 6 months after primary cancer (31), thus excluding the initial 6 months of follow-up. On the other hand most studies make a distinction between tumors diagnosed close together (synchronous) vs far apart (metachronous) (32). How these entities are defined varies. Some studies used 6 months between first and second tumor (31, 33, 34) while some used 3 months (35). A few studies even used 1-2 years between 1st and 2nd cancer (35). Second primary breast cancers diagnosed in the same breast are considered ipsilateral breast cancer and are traditionally not included under the common definition of bilateral breast cancer.

There are an estimated 2.2 million women living in the US who have been diagnosed at some time with breast cancer (1), the corresponding figure in Sweden is 73,000 women, all of whom are at risk one yet one more breast cancer. Approximately 0.7 % of all breast cancer cases will annually develop a second bilateral breast cancer (6) a disease that has been estimated to represent between 2-11% of all breast cancer cases (35). Hence, optimal surveillance and clinical management of women who have had one or two primary breast cancers is a challenge. However, there are only limited data on incidence rates of synchronous and metachronous breast cancer (6, 35), results on temporal trends in incidence are conflicting (31). The risk has been reported as independent (constant) from the time of diagnosis of the primary cancer (35). The large range in the cumulative risk estimate is due to differences in sample size, age range and follow-up (5, 35-38).

There are few identified risk factors of bilateral breast cancer, the most important being early age at onset of the initial breast cancer (5, 34, 39) and family history of breast cancer (34, 36, 39). The association between menopausal status and the risk of breast cancer in high risk groups, such as bilateral breast cancer remain poorly characterized. There are also several studies on the association of lobular histology (35), reproductive factors (40, 41), body weight (40, 42) and several other risk factors (37, 40, 41) on the risk of bilateral breast cancer but the findings are often difficult to interpret due to contradictory results and small sample sizes resulting in poor statistical precision. The risk of bilateral breast cancer is probably even more genetically determined than unilateral cancer and to a lesser extent influenced by mammography screening and HRT but to some degree dependant on given adjuvant therapy. Interestingly, only 5 percent of all bilateral breast cancer cases are mutation carriers for the high penetrance genes BRCA1 and BRCA 2 (43).There are several studies suggesting that low penetrant genes must be associated with increased susceptibility of bilateral disease, but to date few candidates have been identified with the exception of the CHEK2 1100 deletion (44).

Radiotherapy following breast cancer has been shown to increase the risk of bilateral breast cancer 10 years following the primary tumor (45), although results are conflicting (46). A reduction of bilateral breast cancer incidence by 30-50% has been seen after

adjuvant systemic therapy (47-51), further complicating the interpretation of risk factors and incidence patterns of bilateral breast cancer. A large population based study in the US has recently reported decreasing rates of bilateral breast cancer in the last decades (38). However, in a study from Canada no calendar effect was observed, perhaps due to differences between the US and Canada in the use of adjuvant treatment (31). The potential risk reducing effects of these treatment regimes have not yet been identified in Sweden on a population level. Particularly it is not known how treatment of primary breast cancer affects outcome of the second primary cancer.

Finding the etiology of breast cancer

Breast carcinogenesis involves several steps (52). The maintenance of genomic integrity requires the coordinated regulation of DNA replication, DNA damage signalling, cell cycle checkpoints and DNA repair. Disturbances in these essential cellular functions due to germ-line mutations may dramatically increase the risk of developing cancer. In short, when the balance between cell proliferation and apoptosis is not maintained, a cancer will develop.

Despite extensive research within the field of breast cancer the etiology of the disease remains largely unknown. Identification of further genes, besides known high penetrant mutations, would greatly improve diagnostic methods for identification of women that are at risk of developing the disease (44). This in turn would allow for effective preventive measures and intervention on a large scale to take place. Women with bilateral breast cancers may be very suitable for the identification of new genetic markers and provide a greater chance of succeeding in that endeavor. It is likely that women with bilateral disease have more of the genetic prerequisites for developing breast cancer, i.e. as indicated by the high and constant risk of bilateral disease from onset of the primary breast cancer. The constant risk suggests that the prerequisites to develop one more breast cancer are already present and could be due to congenital germ-line polymorphisms. It is reasonable to assume that both environmental and genetic risk factors for disease ought to be more pronounced in women with two breast cancers compared to women with just one. Women with bilateral breast cancer could be looked upon as a susceptible subgroup and thus a good candidate for characterizing risk factors for breast cancer. Identifying when and why women are at high risk of a bilateral breast cancer might have far reaching consequences.

Of known risk factors for breast cancer some risk factors stand out as more important than others, ie mammographic density and family history, but for the majority of the remaining identified as well as unidentified factors the conveyed risk is not substantial (23, 53, 54). This leads to thinking of other models for verifying known and identifying new factors. The study population for the vast majority of these studies has been women with unilateral breast cancer. If one instead focus on women with an even higher risk of breast cancer, namely women with bilateral disease it may be more useful for identifying risk factors for breast cancer, especially if the comparison group is one with low risk, ie healthy women. Previous studies of bilateral breast cancer were designed women with unilateral cancer as comparison, resulting in characterizing the excess risk between the two groups (35).

Clinical aspects

The care of women with suspicion of or a manifest breast cancer will in most areas of Sweden be done in a multiprofessional setting, including a surgeon, oncologist, pathologist and radiologist. The care will follow national guidelines including attention to individual requests and patient characteristics requiring deviation from the guidelines. The diagnostic procedure for suspected malignant lesion in the breast is standardized. All patients will undergo three procedures including palpation, mammography and cytology, this triad of investigations has been implemented since the mid seventies in Sweden (55). Clinical mammography was introduced in the early 1960's and by 1980 mammography screening was introduced throughout the country as a consequence of several randomized clinical trail showing a significant mortality reduction among screened women (56, 57).

Treatment

Surgery has always been the primary treatment for breast cancer and is so today. Breast conserving therapy has become the gold standard since the 1990's (46), since it was demonstrated that breast conserving surgery in combination with radiotherapy is as safe and effective as traditional mastectomy (58, 59). Breast conserving therapy is selected for single tumors, less than 4 cm and located in the peripheral part of the breast. About 2-thirds of all procedures today are breast conserving surgery (60).

Axillary node dissection was early recognized as an important adjunct to breast surgery for staging (61). The aim is to remove 10 lymph nodes. Surgery of the axilla is associated with significant morbidity, primarily in the form of lymphedeoma. With the progression of diagnostic modalities tumors were being diagnosed smaller and a larger proportion of the axillary clearances were negative. This sparked the introduction of sentinel node biopsy where by means of a radioactive compound injected in the skin above the tumor or in the border of the areola, the radioactive 'first' or sentinel node in the axilla could be identified. During surgery this node was identified and frozen section preformed, if positive subsequent clearance of the axilla was preformed. Sentinel node biopsy has been shown to be as safe and effective as axillary clearance (62, 63) without the complications of nerve injuries and lymphedema.

Adjuvant therapy

Surgery alone in most cases is not sufficient for optimal management of breast cancer. Radiotherapy as stated earlier is necessary when performing breast conserving surgery. Radiotherapy is given to women with high risk of locoregional recurrence at age less than 60 years. It is commonly administered fractionated by 2 Grays/day with a total of 50 Gray (64).

Endocrine therapy is the second cornerstone of adjuvant therapy. Several randomized trails have demonstrated improved survival, decreased local recurrences and fewer second primary breast cancers (59) as a consequence of endocrine therapy. It started historically as ovarian ablation (65) and has evolved into anti-estrogen therapy (Tamoxifen®) introduced in 1980's. Standard duration of therapy today is 5 years (47,

51). Tamoxifen is still readily used for ER positive tumors and has received a complement by aromatase inhibitors during the last decade. Aromatase inhibitors have been demonstrated to a convey improved survival (66) but are yet reserved for high risk groups primarily due to cost aspects.

The final group of adjuvant therapy is chemotherapy. Chemotherapy is selected for women age 70 years or less with high risk for metastatic disease. Traditionally anthracyclin based regimes have been used and recently taxane based regimes have been introduced. Chemotherapy in the adjuvant setting has been shown to reduce mortality by about 20% (59).

A Darwinian selection model of tumor survival: Therapeutic resistance

As breast cancer is prevented (67) and breast cancer prognosis is continuously improving by means of more aggressive therapy, an increasing issue is the possible effect that adjuvant therapy has on tumor selection. There is increasing evidence that women having received adjuvant chemotherapy for the primary cancer develop more aggressive local recurrences (68). Furthermore, it has also being shown that adjuvant hormonal therapy of the primary cancer predicts estrogen receptor status of the second primary (69). This leads to the consideration of having to take into account how a woman was treated for her primary cancer if she develops a local recurrence, distant metastasis or even a new primary tumor in the opposite breast. One can conceive of a situation where adjuvant therapy eradicates less malignant clones, leaving more aggressive tumors to surface later.

Most studies to date use in vitro models to study therapeutic resistance (70, 71). Women with bilateral breast cancer offer a natural in vivo model to study how adjuvant therapy might influence the occurrence of new malignant clones. Adjuvant therapy could be viewed as a double edged sword with known positive effects, ie reducing not only local recurrences, distant metastasis but also new primaries in the opposite breast. Simultaneously adjuvant therapy may, in a Darwinian fashion, serve to selectively allow more malignant clones to surface. This idea would be testable when one would study the occurrence of second primary cancers during adjuvant therapy of the first vs the occurrence of tumors not subjected adjuvant therapy.

Familial breast cancer risk

Studies on familial aggregation of breast cancer cases place family history as one of the strongest risk factor known for the disease (15) ; a recent study reanalyzed 52 epidemiological studies on familial breast cancer and presented summary risk ratios of 1.80 and 2.93 for one and two affected first-degree relatives, respectively (7). In recently published studies, based on the Swedish Family Cancer database, it is estimated that 25% of breast cancer cases have a genetic background (72, 73). A strong family history for breast cancer is associated with an 80% absolute risk before 70 years of age. In the clinical setting family history for breast cancer is defined as familial aggregation of breast cancer cases (three or more cases in the same branch of the family, at least one of which occurs prior to age 50) that is explained by a dominant genetic pattern. In population based studies a family history is defined as having one first degree family member with

the disease. Conventional risk assessment of the disease in unaffected women focuses on traditional risk factors such as age of onset and the number of family members with breast cancer using several models (74-76). Often genetic counseling also includes mutation screening of the high penetrant BRCA 1 and BRCA 2 genes (19, 77).

A number of genes associated with hereditary forms of breast cancer have been identified. BRCA 1 was the first gene to be identified (20) followed by BRCA 2 a couple of years later. Mutations in these two genes are also associated with ovarian cancer. Further hereditary forms of breast cancer are linked with the "Li-Fraumeni-syndrome", a congenital defect in the p53-gene, and mutations in the ataxia-telangiectasia gene (ATM).

Mutations in the dominant and highly penetrant BRCA 1 and 2 genes drastically increase the risk of breast cancer. Still, these mutations only account for 1-2% of all breast cancer cases and there is most likely a much larger subgroup of women who have germline polymorphisms in many genes of low penetrance. These polymorphisms could potentially lead to an increased risk of developing breast cancer and women with bilateral disease could theoretically be carriers of germ-line mutations in these genes.

A disease in a susceptible subgroup of women?

There is increasing evidence that breast cancer primarily is a disease of a susceptible minority of women (78-80). This belief is based on several observations, the first being the fact that a healthy woman has a highly age-dependant risk of the disease (2), while a woman with a first primary breast cancer has a considerably higher age-independent risk of another breast cancer in the contralateral breast (38, 81). Secondly, the risk of disease in the monozygotic twin sister of a breast cancer patient seem to be comparable to the risk of bilateral breast cancer (78). Thirdly, whereas the familial risks for most cancer types increases multiplicatively with the number of first-degree relatives that are affected by the disease, this has not been observed for breast cancer, where the familial risk is seemingly much less related to the number of affected relatives (8, 82). Fourth and finally, there is increasing evidence that the breast cancer etiology is polygenic, and as such it seems that a small proportion of the population carry the majority of the risk (80). Together these findings suggest that breast cancer may originate from only a small proportion of the female population, leaving the vast majority of women with little or no risk.

A biological model of bilateral disease: Breast cancer in twins

Studies of twins are interesting since they allow, among several things, observations of the importance of degree of shared genome, where dizygotic twin pairs have the same genomic variability as any two sisters or a mother-daughter pair and where monozygotic pairs share 100% of their genome (73). Studies of twins also allow for the assessment of the risk of disease by age and time since diagnosis simultaneously. There are similarities in the study of risk of a primary cancer in the opposite breast and the risk of cancer in a twin sister, with the one obvious difference being the number of breast at risk, ie one vs two. Furthermore in studies of familial breast cancer bilateral breast cancer could be used

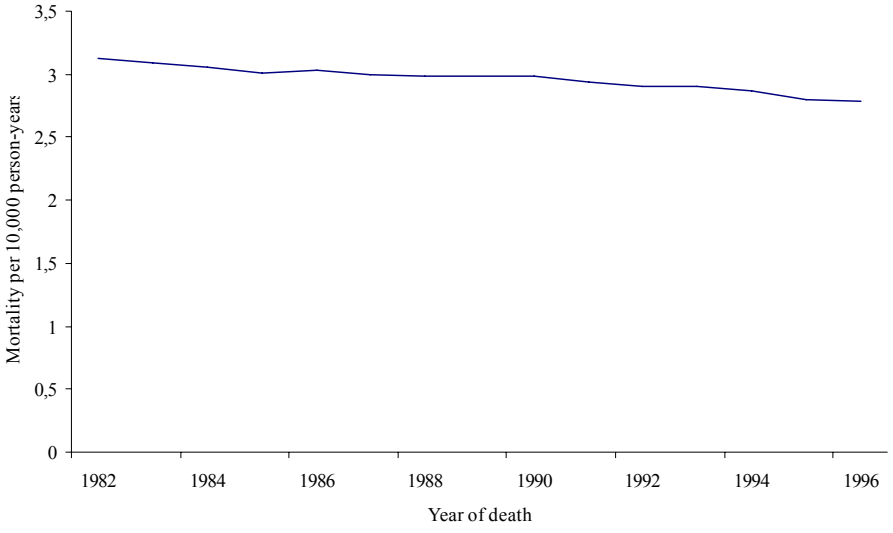
as a model to understand familial breast cancer since the host of the first and second cancer is one and the same and therefore related to a 100%. In parallel to twin studies women with bilateral disease also allow for the assessment of age and time since diagnosis simultaneously. These similarities allow for the possibility of interesting comparative studies between the breast cancer occurrence among twin pairs and bilateral disease (78).

Prognosis of breast cancer

Unilateral breast cancer prognosis

The survival of women with breast cancer has also been increasing during the last decades, although not of the same magnitude as the increase in incidence (Figure 2 and 3). Improved survival is attributed to the interventions of mammography screening and the introduction of adjuvant therapy (radiation, hormonal and chemotherapy) (59, 83). Surprisingly breast cancer survival is not very age dependant (84). The expected 5-year survival of women diagnosed today with breast cancer is approaching 85% (85). In contrast to the global variations in incidence there are smaller differences in breast cancer mortality world wide (Figure 4).

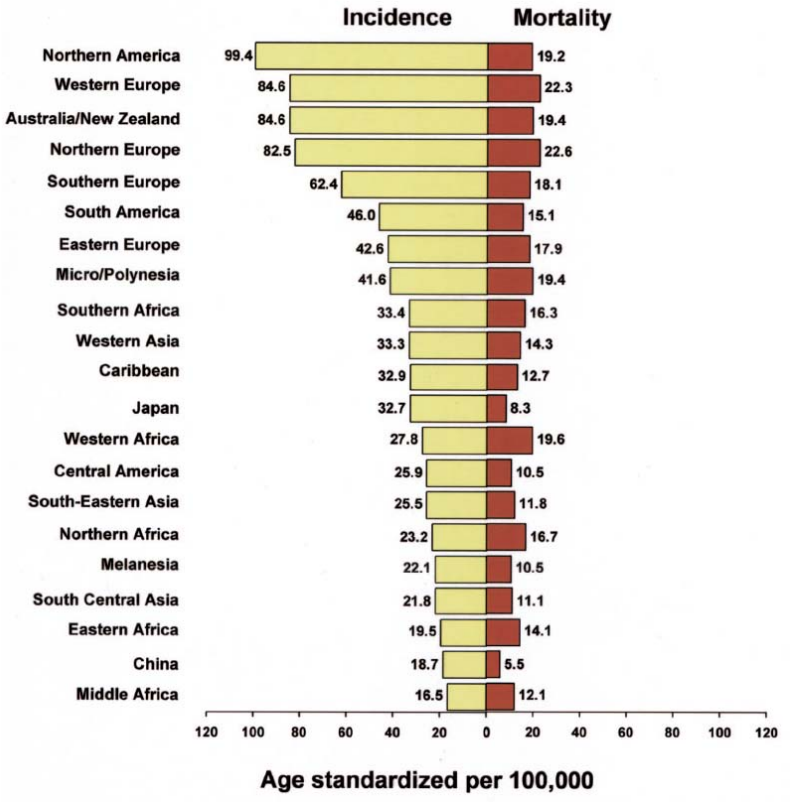
Figure 3. Trends in female breast cancer mortality in Sweden. Data from the Swedish Cancer Register



The ultimate goal for any clinician is to have a prognostic tool that truly reflects the biological aggressiveness of the tumor (86). This is unfortunately a very rare situation. Instead there are to date many clinical covariates that to some degree predict survival of a woman diagnosed with breast cancer. A tumor will develop by means of clonal expansion and at some arbitrary point become detectable. It will eventually produce symptoms, ie palpable mass and subsequently lead to death by means of metastatic disease (Figure 5). Assessing changes in survival over time can become very complicated, especially in an

environment where breast cancer screening is implemented, since any intervention that leads to an earlier diagnosis introduces an artificially increased survival time or lead time. The goal of earlier detection is postponed death, which then becomes difficult to measure.

Figure 4. Incidence and mortality of breast cancer world wide, adapted from Ferlay at al, 2005.



Stage is the most commonly used prognosticator (86). Stage, of which tumor size is one parameter, possesses both the measure of lead time as well as tumor aggressiveness (Figure 6). As seen in Figure 6 it is difficult to differentiate slow from fast growing tumors at the time of diagnosis. In recent years the introduction markers of tumor cell activity, that do not posses the difficulty of lead time, have been introduced as prognosticators including measures of cellular proliferation (87) and gene amplification, HER-2 neu (88). Some clinical factors are referred to as therapy predictors, since they allow the clinician the choice of a specific therapy. Estrogen and progesterone receptor status and HER-2 neu are three such examples (59, 89). There is though some evidence to indicate that receptor status also can serve as prognosticators (90, 91). There are also known risk factors for the disease that are associated with outcome such as HRT (92, 93) and weight (94).

Figure 5. Time considerations in the natural history of a malignant disease (Adapted from Paul Dickman).

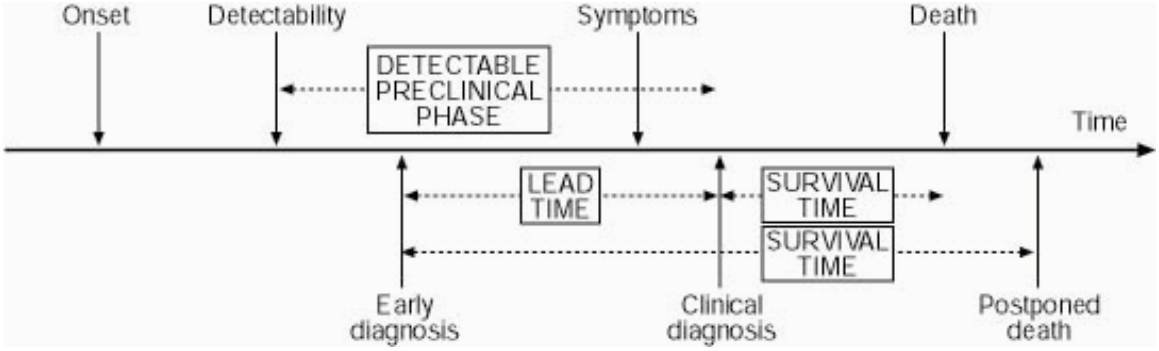
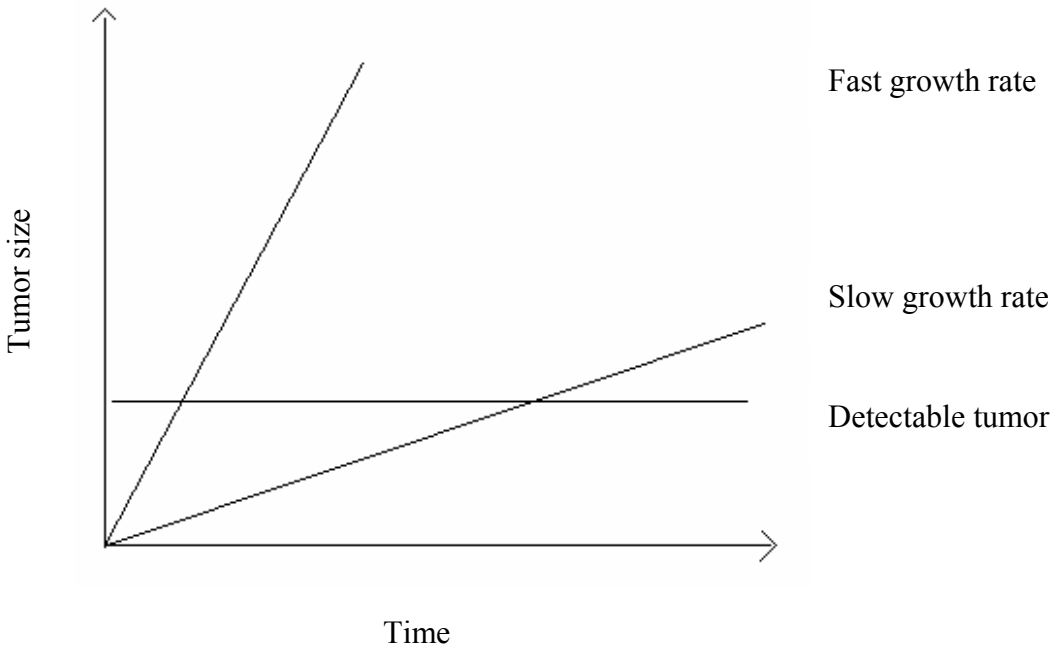


Figure 6. Clinical detectability vs lead time



Bilateral breast cancer prognosis

Bilateral breast cancer prognosis is little studied and even less is known about the prognostic outlook following treatment of a second primary cancer (95, 96). Bilateral breast cancer prognosis studies are often very small, usually with a sample size smaller than 200 women. Futhermore, the studies do not commenly use a population based design, making them difficult to interpret (97). Comparing results of bilateral breast cancer survival studies is also difficult, not only because of definitions of the disease and

study populations but also due to important methodological aspect of when to start follow-up for women who develop a second cancer. The woman has to survive the first cancer to develop a second and therefore most but far from all studies start follow-up at the second cancer diagnosis (97). Heinävaara et al. proposed various models to appropriately take into account the time between first and second cancer when comparing the survival between individuals with one vs two cancers (98). The prognostic outlook among patients with bilateral breast cancer has been reported to be worse than among those with unilateral cancer (96, 99), but several studies report no difference in survival (100, 101) An additive effect of two forces of mortality has been suggested as an explanation for the observed excess mortality among women with bilateral disease compared to women with unilateral disease (96). There is limited information on bilateral cancer prognosticators, but as for unilateral cancer, stage and grade predict outcome of disease (96, 97, 100). Young age of onset and short time between the first and the second primary cancer are associated with poor outcome (95, 96). Women treated with tamoxifen are more likely to develop oestrogen receptor negative second primary tumor (69, 102).

The possibility of misclassified metastatic disease is a concern, but it is by most studies considered to be a minor problem (103). In studies of the occurrence of bilateral breast cancer, distant metastasis misclassified as new primary cancers would result in elevated and distorted incidence patterns. On the other hand, in studies of bilateral breast cancer prognosis if a proportion of bilateral cancers are distant metastasis misclassified as new primary cancers it would decrease survival for women with bilateral disease. More importantly misclassified metastatic disease would have strong clinical implications. A metastasis in the contralateral breast would be a TNM stage IV cancer while a misclassified new primary cancer would appear to be a node negative TNM stage I cancer. The treatment of women with TMN stage I and IV cancer are of course very different.

Familial breast cancer prognosis

The prognosis of women with a family history of breast cancer has been reported as similar or worse compared to women without a family history (104-106). A relatively poor outcome among women with fatal breast cancer may arise primarily due to ER-negative tumors among BRCA 1 positive women (106). With few exceptions, hormone replacement therapy being one of them (92), risk factors for breast cancer have not been associated with prognosis (12, 107) .
Since risk of the breast cancer can be inherited, why can not prognosis of the disease be inherited? There is increasing evidence that prognosis is not only determined by tumor characteristics, but in part determined by germline genetic variation (108, 109). The majority of the scientific evidence originates from different animal models such as mouse (110), while it has not been clearly demonstrated a correlation in breast cancer survival among first degree family members. It does therefore seem plausible that the metastatic potential in a tumor and thus the prognosis is determined by the interaction of tumor and host characteristics (111, 112).

During clinical counseling for women with a family history of breast cancer two risk models are primarily used by Gail et al. and Colditz et al.(74-76). Both models focus on assessing the lifetime risk of breast cancer for the woman by gathering clinical covariates, such as number of family members affected, age at menarche and menopause etc. Little is known of whether additional information on the outcome of the first degree family member actually predicts outcome in the woman seeking clinical counseling. It is conceivable that this may be the case since germline genetic variation has been associated with breast cancer outcome (113).

Aims

The aim of this thesis was to study the risk and prognosis of breast cancer using the high risk groups of women with bilateral and familial breast cancer. We pursued the task in the following manner:

1. By characterizing the incidence of synchronous and metachronous bilateral breast cancer in Sweden by age and time since diagnosis of first cancer.

2. By characterizing how incidence and prognosis of bilateral breast cancer in Sweden from 1970 to 2000 has changed and if these changes were dependant on age at diagnosis and treatment of the primary cancer.

3. By comparing the risk of cancer in the opposite breast by family history and in Scandinavian twin sisters to breast cancer patients by zygosity.

4. By investigating if the prognosis of breast cancer might be inherited.

Subjects and Methods

Swedish Cancer Register

The nation-wide Swedish Cancer Register was established in 1958. Reporting to the register of all newly diagnosed malignant diseases is mandatory both for clinicians and for pathologists and the register is estimated to be at least 98% complete (114). For each notified cancer, the register includes the individually unique national registration number, ICD-code and date of diagnosis. Information on stage of disease and treatment is not included in the Swedish Cancer Register. Using the national registration number, the Cancer Register can be linked to the nation-wide Cause of Death Register and information on immigration and emigration in the Total Population Register. Thus complete follow-up can be obtained for the vital status of all individuals notified to the Cancer Registry.

Total Population Register

The Total Population Register provides information the number and place of residency of all Swedish residents. It is updated yearly and holds additional information on date of immigration as well as emigration.

The Cause of Death Register

The nation-wide Swedish Cause of Death Register holds information on date and cause of death on all Swedish residents. Cause of death is ascertained from death certificates filled in by treating physicians. The quality of the cause of death registration is reportedly high (115).

Stockholm Regional Oncological Center

Since 1976 all new primary breast cancers in the Stockholm-Gotland Health Care Region have been reported to a central regional breast cancer register (*http://www.sll.se/oc*). The register holds information on the individually unique national registration number, ICD-code and date of diagnosis, stage, estrogen receptor status, and adjuvant treatment.

The Multi-Generation Register

The Multi-Generation Register includes all Swedish residents born after 1931, who were alive in 1960, and all those born thereafter. It contains links between children and parents through their national registration numbers assigned to all residents in Sweden. The register is updated yearly. During the period 1961-2001 the completeness of the Multi-Generation Register became progressively better and from 1991 it is considered complete (116). Therefore among individuals who died before 1991 notification of their mothers in the Multi-Generation Register has some degree of missingness.

The Scandinavian twin registries

Swedish Twins

The Swedish Twin Register consists of two birth cohorts (117) of which the first was made up of 10,503 pairs of twins of the same sex who were alive in 1961, and who were born during the period 1886 through 1925. The second of the two cohorts consists of 12,883 pairs of twins of the same sex born 1926 through 1958. The study cohort was linked to the Swedish Cancer Register (2). Complete follow-up and assessment of vital status was achieved by means of linkage to the Cause of Death Register and linkage to the Register of the Total Population that holds information on emigration and immigration.

Danish Twins

The Danish Twin Register established in 1954 holds data on 8,461 pairs of twins of the same sex with known zygosity who were born between 1870 and 1930. The register included all twins born in Denmark from 1870 through 1910, (118) and was later expanded to include twins of the same sex born from 1911 through 1930 (118-120). All pairs of twins who both survived to the age of six years are included in the register. Vital status was assessed annually through 1979 with information from the Central Register of Deaths. After 1979 vital status was regularly updated by linkage to the Civil Registration System, which includes all persons living in Denmark since April 1, 1968. The Danish Cancer Register records information on breast cancer diagnosed in Denmark since 1943 (121-123). All twin pairs of the same sex where both were alive on January 1, 1943, have been linked to the Cancer Register for the period from 1943 through 1998.

Finnish Twins

The Finnish twin cohort compiled from the Central Population Register in 1974 includes 12,941 pairs of twins who were born from 1880 through 1958 and who were both living in Finland on December 31, 1975 (124). Breast cancers that were diagnosed among the Finnish twins from 1976 through 1996 were identified by linkage to National Cancer Register data using the personal identification number assigned to every resident of Finland. The Register has information on breast cancer diagnosed in Finland since 1953 (125). In addition, the study cohort was linked to the Central Population Register to obtain data on death and emigration.

Determination of Zygosity

Zygostity was determined by questionnaires that have been shown in validation studies for all three national cohorts to classify more than 95% of pairs of twins correctly (119, 126, 127).

Main measures used in a cohort design

Incidence rates

For the study of bilateral breast cancer in Paper I-III we identified all women diagnosed with breast cancers during 1970-2000 (Paper III; 2002) using several national registers. Women having pre-malignant conditions or cancer in situ were not included in the study. We excluded women for whom the history of breast cancer was uncertain because they had immigrated to Sweden and women who had a malignant tumour other than in the breast prior to the first breast cancer. Second primary breast cancers were categorized as synchronous bilateral breast cancers if diagnosed within three months of the first primary cancer and as metachronous breast cancers if diagnosed more than 3 months following the diagnosis of the first primary cancer. Synchronous bilateral breast cancer was regarded as a simultaneous clinical event, and thus the incidence was calculated as for unilateral breast cancer using the Swedish female population counts.

The incidence rate of metachronous breast cancer was calculated using as denominators the accumulated person-years at risk among women with unilateral breast cancer. The person-time at risk started 3 months after the date of diagnosis of first breast cancer and continued until diagnosis of bilateral breast cancer or a diagnosis of any other malignant disease, emigration, death, or end of follow-up (Paper I-II: December 31, 2000; Paper III December 31, 2002), whichever came first. We have chosen this design to facilitate a starting point of when a woman is at actual risk of an event and at the same time use a population that is actually at risk of that same event. The net result, as outlined above, was 2 different populations at risk for metachronous and synchronous bilateral cancer. For validation reasons the rates for synchronous cancers were also calculated using as denominator women with unilateral breast cancer. The trend for these rates by both age and calendar period were similar to those using population counts.

The incidence rate of breast cancer in twin pairs in Paper III was calculated as the ratio of the number of new cases to the accumulated person-years at risk in the twin siblings of women with breast cancer. The unaffected twin sisters were followed from the date of the first twin sisters (index) diagnosis of breast cancer to the date of diagnosis of breast cancer in the second twin sister or to the diagnosis of another malignant cancer, emigration, death, or end of follow-up (Sweden; December 31, 2002, Denmark; December 31, 1998, Finland; December 31, 2005), whichever came first.

In Paper III from a total population cohort comprising about 11 million individuals recorded in the Multi-Generation Register we identified female offspring born in Sweden since 1932 with a first primary invasive breast cancer diagnosed during 1961-2001. Subsequently, we identified all mothers and sisters to these women who were also born in Sweden and had been diagnosed with a first primary invasive breast cancer during the same period. We excluded all women for whom the history of breast cancer was uncertain because they had immigrated to Sweden and all women with any primary malignant tumor other than a breast cancer prior to the first breast cancer. From this study population incidence rates for bilateral disease was calculated as outlined above from the breast cancer cohort from the Swedish Cancer Register.

Standardized incidence rates

Standardized incidence rates provided a measure of occurrence that is standardized or weighted against weighted sum of reference rates using the stratum specific person-times of the study group as weights (128). For metachronous bilateral breast cancer in Paper I, standardized incidence ratios (SIRs) were calculated as the ratio of the observed/expected number of cases during the follow-up period. The expected number of bilateral breast cancers was calculated using person years accumulated by the unilateral breast cancer cases, multiplied by the age- and calendar-period-specific unilateral breast cancer incidence rates as reference. The unilateral breast cancer incidence rates were calculated using the Swedish female population counts in 5-year age and calendar period groups. Thus, the SIR provides a comparison of the calendar-adjusted risk of bilateral breast cancer relative to unilateral breast cancer in the same age group.

Cumulative measures of occurrence

In Paper I and III we also used Nelson-Aalen estimates for graphical displays of cumulative incidence (129) and a log-rank test was performed between age strata (Paper I). The estimates are a result of 1- log of 'the survival' proportion, thus generating a cumulative estimate at any time interval since start of follow-up.

Mortality rates

Deaths due to breast cancer were ascertained from the Cause of Death Register. The mortality rates uni- and bilateral disease in Paper II were calculated with the accumulated person-time at risk as the denominator. This time started at first diagnosis for unilateral and at second diagnosis for bilateral breast cancer and continued until diagnosis of bilateral cancer (for unilateral cancer), emigration, death, or end of follow-up (December 31, 2000), whichever came first. When to start the time at risk to die following a diagnosis of a second primary cancer is not entirely clear and it depends on the research question that is being addressed. A woman has to survive her primary cancer long enough to develop the second primary resulting in no deaths prior to that event. We wanted to answer the question of a woman with a history of the disease risk to die following a second primary breast cancer. In this setting we decided to start follow-up from the diagnosis of the second primary malignancy. We censored follow-up at age 80 years because classification of cause of death may become less reliable in older women.

The analysis of familial breast cancer deaths in Paper IV was based on breast cancer specific mortality among patients with an affected mother or sister (proband). We limited the outcome estimate to 5 years because it is a clinically accepted estimate of prognosis. The person-time at risk started at the date of first diagnosis of breast cancer and continued until emigration, end of follow-up (December 31, 2001) or death, whichever came first. In the sister pair analysis the oldest sister was chosen as proband for reasons of better statistical power by an approximately equal number of deaths between the sister pairs.

Cumulative measures of death

The Kaplan-Meier method was used in Paper IV to estimate survival proportions and we also used the Nelson-Aalen method to estimate cause specific cumulative mortality (Paper II). In Paper IV we compare survival between first degree relatives using the Kaplan-Meier method by crudely grouping the proband (mother or sister) into either dead due to breast cancer within 5 years of diagnosis or alive five years after diagnosis. Due to the end of follow-up of the register in December 2001 we restricted the date of diagnosis until 1996 to ensure that all probands had the possibility of five year survival.
The Kaplan-Meier method has long been the gold standard for graphical displays of survival data. Describing cause-specific mortality using the Kaplan-Meier plot is not entirely easy, since it gives a survival proportion of individuals that did not die from breast cancer and not of women who are actually alive. The Nelson-Aalen method is therefore more straightforward in presenting the proportion that actually died from the disease with a certain follow-up. The Kaplan-Meier plot for a cause specific event may erroneously be interpreted as disease free survival which it is not.

Incidence rate ratios

In Paper I-III Poisson regression modeling was used for modeling bilateral breast cancer occurrence adjusted for age-, calendar period and time since diagnosis of primary cancer. The Poisson model uses the logarithm of time at risk and provides rate ratios that describe the relative difference in occurrence between for example unilateral and bilateral breast cancer taking possible confounders into account. In Paper III we also used Poisson regression to model the relative risk of breast cancer comparing the incidence rates of bilateral breast cancer and the incidence rate of breast cancer in the unaffected twin sisters adjusted for country, age and calendar period of diagnosis.

Mortality rate ratios

In Paper II Poisson regression modeling was used for modeling breast cancer survival. The main measure from a Poisson survival model is mortality rate ratio, which describes the relative difference in survival between 2 categories with possible adjustment for confounders. We used Poisson regression to estimate how mortality following bilateral breast cancer is affected by age at diagnosis of the first cancer and time interval to diagnosis of second breast cancer with adjustment for calendar period. In the validation cohort Stockholm Regional Oncological Center further adjustment for TNM stage, estrogen receptor status (negative<0.05 fmol/µg DNA) and adjuvant treatment could be made.

Hazard ratios

Our ultimate aim in Paper IV was to model the prognosis of the daughters and sisters as a function of the prognosis of the proband (mother or older sister respectively).This was accomplished by linking two separate survival models together. This ‘linkage’ was possible using multivariable (Cox) proportional hazards models. We first needed to classify the prognosis of the proband, which we did based on the deviance residual from a

Cox model fitted to the proband data adjusting for period and age of diagnosis. The deviance residual provides a measure of how the survival of the proband compares to other probands with the same age and year of diagnosis. Since the residual is calculated as observed minus expected mortality, values below, above and around zero correspond to better, worse or as expected prognosis, respectively. The deviance residuals are more symmetrically distributed about zero than the unadjusted (crude) residuals. We were not able to use a Poisson regression model in this analysis since there was no obvious way to provide a single residual for a single subject (woman). Instead the Poisson model provides one residual for every stratum of the covariates in the model and these residuals are not easily combinable. We defined the good prognosis group as the first tertile of the deviance residual distribution, the medium prognosis group as the second tertile and the poor prognosis group as the third tertile. Finally, the association between the cause-specific hazard in the daughters or sisters and probands prognosis was investigated employing a proportional hazards model adjusting for all available confounders such as age and calendar period of diagnosis, parity, age at first birth, socioeconomic factors and area of residence at diagnosis.

Results

Bilateral breast cancer risk

Although breast cancer is the most common female malignancy, bilateral breast cancer remains little studied. Primarily because it is not very common and the disease requires complete and long follow-up to get unbiased estimates on risk and prognosis. We used a large population based data set of 123,757 Swedish women diagnosed with invasive breast cancer 1970-2000 of whom 6,550 developed bilateral breast cancer. Our goal was to estimate the risk of the disease by age, calendar period and time since first cancer.

Overall, about 30% of all bilateral cancers in the cohort were classified as synchronous (diagnosed within 3 months of first primary) (Table 1). Approximately 1.6 synchronous cancers occurred per 10^5 person-years at risk. The age-incidence pattern of synchronous breast cancer seems to mimic the unilateral age pattern, although the absolute rates of synchronous bilateral cancer were 50-100 times lower than those of unilateral (Figure 7). This age pattern was also evident using unilateral breast cancers rather than total population as the denominator (data not shown). Age markedly influenced the incidence rate of metachronous breast cancer. Women diagnosed with the first cancer after the age of 50 years experienced an incidence of $550/10^5$ person-years, in contrast to an almost double rate ($800/10^5$ person-years) for younger women (Figure 7).

The incidence of synchronous cancer increased from 1970 until the mid 80's and remained almost constant thereafter (Figure 8). The incidence rate of metachronous cancer decreased by almost one third over the study period from $640/10^5$ in 1970 to $440/10^5$ in 2000. This overall decreasing trend was similar for metachronous cancers diagnosed within 5 years of the first primary breast cancer.

Bilateral breast cancer prognosis

Using the same cohort we wanted to investigate the prognosis by age, calendar period and time since first cancer and furthermore to asses the importance of stage and treatment on the prognosis of bilateral breast cancer. The 5-year breast cancer specific mortality rate was only modestly related to age at diagnosis among women with unilateral disease at a rate of approximately 50/1000 person-years (Paper II). Following synchronous bilateral breast cancer, mortality decreased from 136 per 10^3 person-years at age <40 years to 73 per 10^3 person-years at age 70-79 years at diagnosis. The modifying effect of age was even more pronounced for metachronous bilateral breast cancer with a more than 3-fold gradient in mortality between women aged <40 years at diagnosis (178 per 10^3 person-years) and those aged 70-79 years at diagnosis (55 per 10^3 person-year).

The 5-year cause-specific mortality rate of synchronous cancer improved continuously during the study period from 124 per 10^3 person-years in 1970-74 to 66 per 10^3 person-years in 1995-2000 (Paper II). Similarly, the 5-year cause-specific mortality rate of metachronous breast cancer improved during follow-up from 143 per 10^3 person-years to 68 per 10^3 person-years. This trend was less obvious for metachronous breast cancer diagnosed less than 5 years since unilateral breast cancer.

Figure 7. Age-specific incidence rates of unilateral, synchronous and metachronous bilateral breast cancer in Sweden 1970-2000. Incidence rates of unilateral and synchronous caner were calculated using the whole population as "population at risk". Incidence rate of metachronous cancer was calculated using women with unilateral breast cancer as "population at risk".

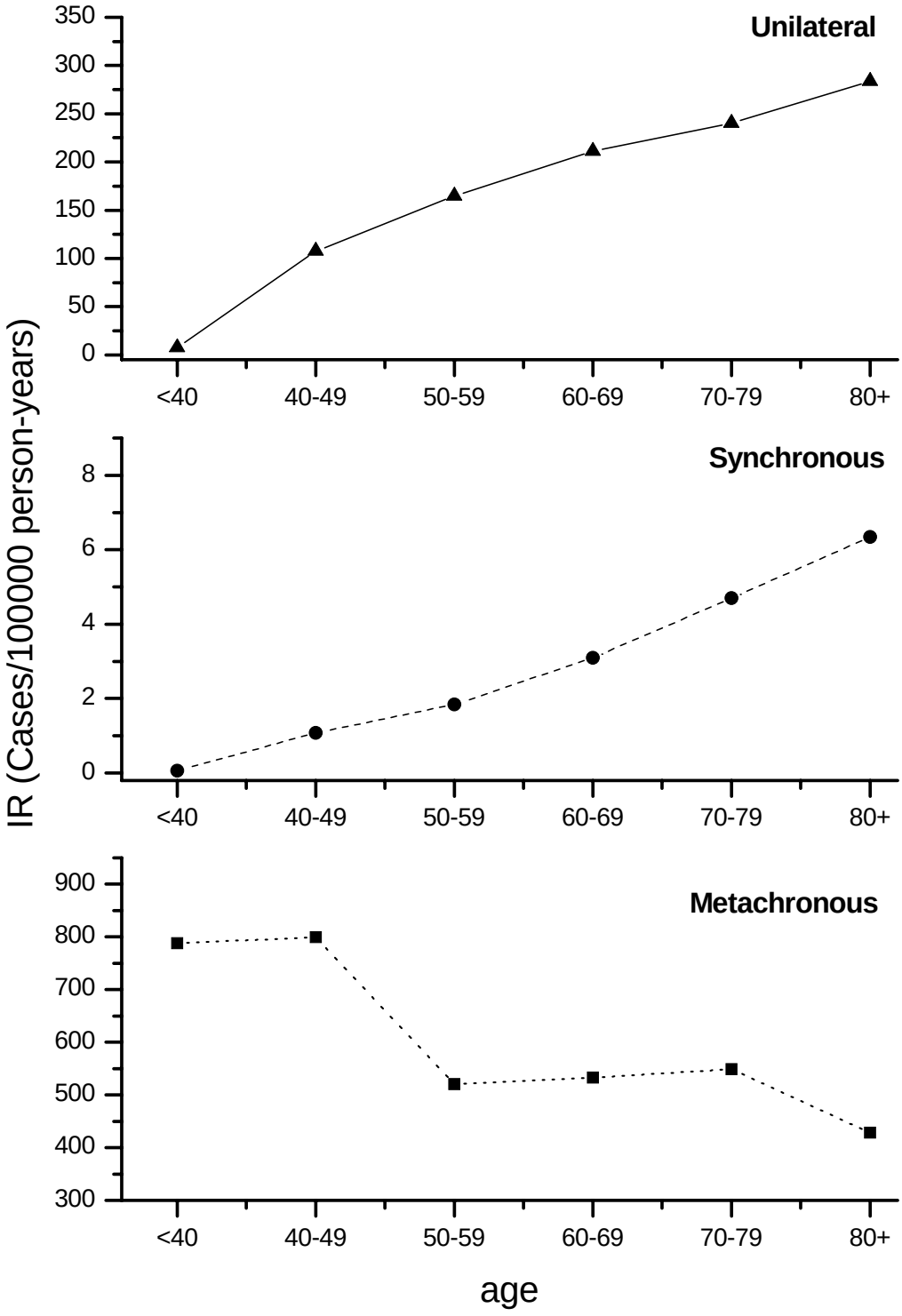


Table 1. Number of unilateral and bilateral breast cancers reported to the Swedish Cancer Register during 1970-2000.

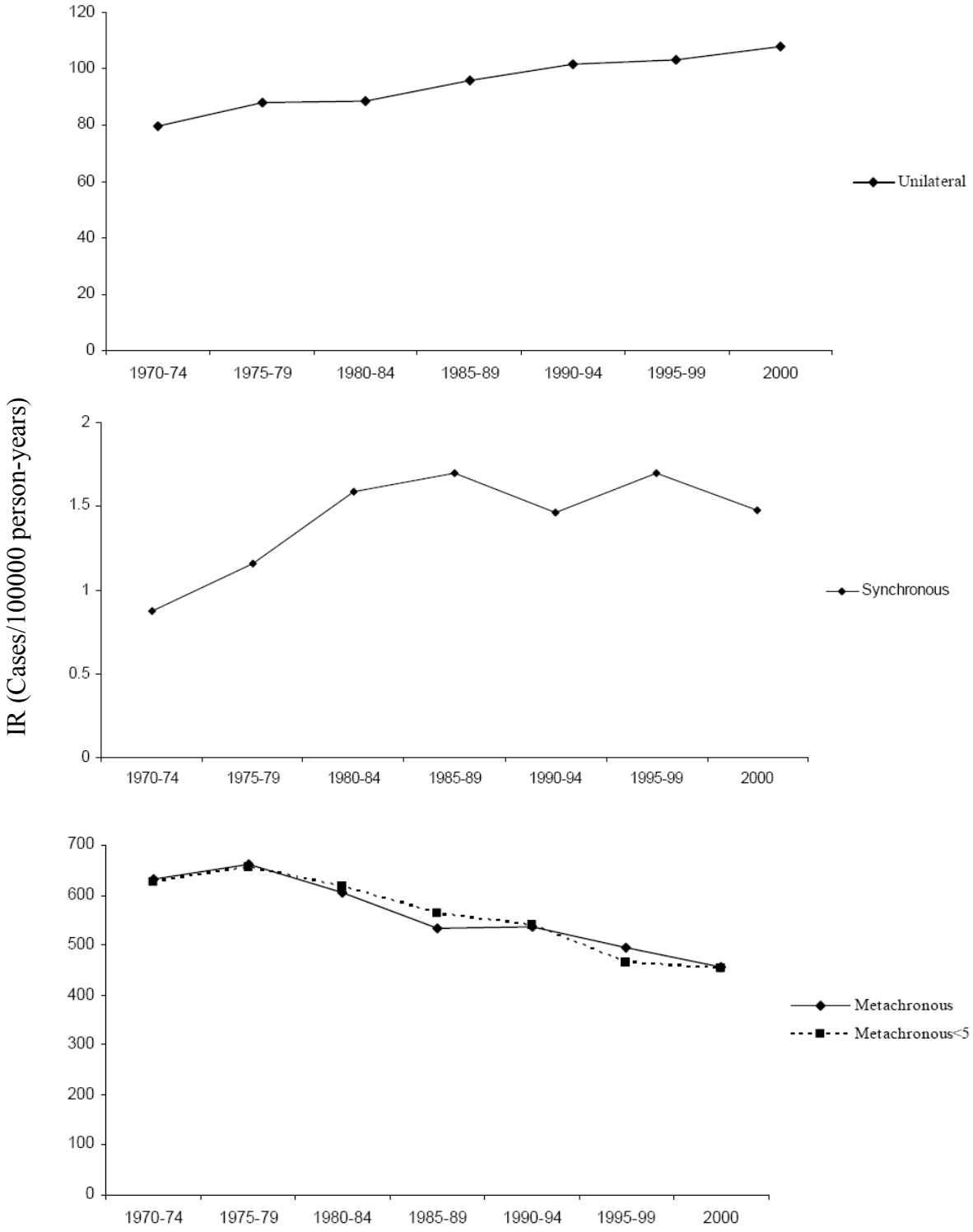
		Age at diagnosis					
Type of breast cancer	Total no.	<40	40-49	50-59	60-69	70-79	80+
Unilateral	123,757	5,298	17,732	25,273	30,007	27,726	17,721
Bilateral[α]	6,550	166	783	1,154	1,591	1,805	1,051
Synchronous[*]	1,893	41	179	282	445	546	400
Metachronous[*]	4,657	125	604	872	1,146	1,259	651

		Year of diagnosis					
	Total no.	1970-74	1975-79	1980-84	1985-89	1990-94	1995+
Unilateral	123,757	15,096	17,022	17,366	19,157	21,288	27,278
Bilateral[α]	6,550	351	759	1,066	1,190	1,341	1,843
Synchronous[*]	1,893	182	242	334	363	324	448
Metachronous[*]	4,657	169	517	732	827	1,017	1,395

[α] Bilateral breast cancers are counted both at the diagnosis of first primary breast cancer and at the subsequent second primary breast cancer.

[*] Synchronous breast cancers were defined as being diagnosed within 3 month of primary breast cancer and the remainder were defined as metachronous breast cancers.

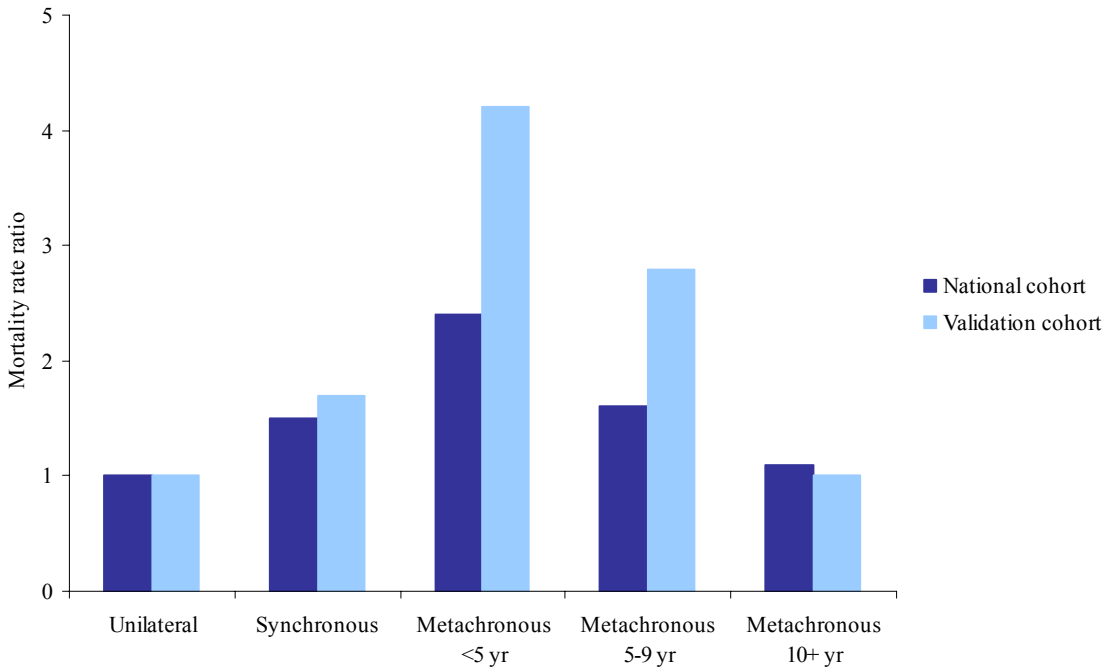
Figure 8. Temporal trends in incidence rates of unilateral, synchronous and metachronous bilateral breast cancer, in Sweden 1970-2000. Incidence rates of unilateral and synchronous caner were calculated using the whole population as "population at risk". Incidence rate of metachronous cancer was calculated using women with unilateral breast cancer as "population at risk".



We used Poisson regression including both the national and the regional validation cohort to estimate how mortality following bilateral breast cancer is affected by time interval to diagnosis of second breast cancer (Figure 9). Women with bilateral metachronous cancers diagnosed more than 10 years after initial diagnosis had a 5-year breast cancer mortality not significantly different to that of women of the same age with a unilateral breast cancer. On the other hand women with bilateral cancer diagnosed less than 5 years after a unilateral diagnosis had a poor prognosis.

Contrary to women with unilateral cancer we observed a lack of improvement in prognosis for women with metachronous disease diagnosed within 5 years of the first cancer (Paper II). We also observed a close to 30% decrease in incidence during 1970-2000 together with an overall very poor prognosis (Figure 8 and 9 and Paper II). These observations suggested to us that perhaps adjuvant therapy is resulting in a decreased risk of disease but leaving more malignant clones to surface later.

Figure 9. Mortality rate ratios from a Poisson model of 5-year cause specific mortality of bilateral breast cancer as compared to unilateral breast cancer by time since unilateral breast cancer diagnosis[*]. In a validation analysis a subcohort of women with TNM stage 1-3 primary cancers from the Stockholm-Gotland Health Care Region was used.



[*]Adjusted for survival time, age and calendar period of diagnosis. [**] Reference: unilateral breast cancer.
[†] The validation cohort was adjusted for time since diagnosis, age at and calendar period of diagnosis, TNM stage, adjuvant treatment, oestrogen receptor status of primary cancer (for unilateral cancer) and second primary cancer (for bilateral cancer).

We tested the hypothesis if women treated aggressively for their first breast cancer were more likely to die when diagnosed with a short latency metachronous cancer using a validation cohort selected from the Stockholm-Gotland Health Care Region (Table 2). Results from our validation cohort supports the interpretation by showing a stage adjusted 2.4-fold higher mortality rate among women who received adjuvant chemotherapy following their first primary breast cancer, while there is no increased mortality following chemotherapy after the second primary cancer. We believe that the findings support a selection process where adjuvant systemic treatment selectively prevents the occurrence of cancers with a favourable prognosis, allowing those with a more aggressive phenotype to surface clinically.

Table 2. Mortality rate ratios (MRR) and 95 percent confidence intervals (CI) – obtained from a Poisson model - of 5-year cause specific mortality among women who developed metachronous bilateral disease within 5 years of their primary breast cancer in relation to adjuvant treatment of primary and second primary cancer. Data from the Stockholm-Gotland Health Care Region.

	Number of women	Type of treatment[†]	Number of deaths	MRR (95% CI)
Therapy of 1st cancer[*]	171	No chemotherapy	50	1.0 ref
TNM stage 1-3[α]	47	Chemotherapy	27	2.4 (1.3-4.4)
Therapy of 2nd cancer[**]	130	No chemotherapy	32	1.0 ref
TNM stage 1-3[α]	50	Chemotherapy	10	1.2 (0.5-2.9)

[α] TNM stage at primary diagnosis. [†] Chemotherapy is defined as exposed to systemic adjuvant chemotherapy with/without hormonal therapy and radiotherapy. No chemotherapy is defined as never exposed to systemic adjuvant chemotherapy. [*]Adjusted for time since diagnosis, age and calendar period of diagnosis, TNM stage of first and second cancer, oestrogen receptor status of first and second cancer and adjuvant treatment of 2nd cancer [**]Adjusted for time since diagnosis, age and calendar period of diagnosis, TNM stage of first and second cancer, oestrogen receptor status of first and second cancer and adjuvant treatment of 1st cancer.

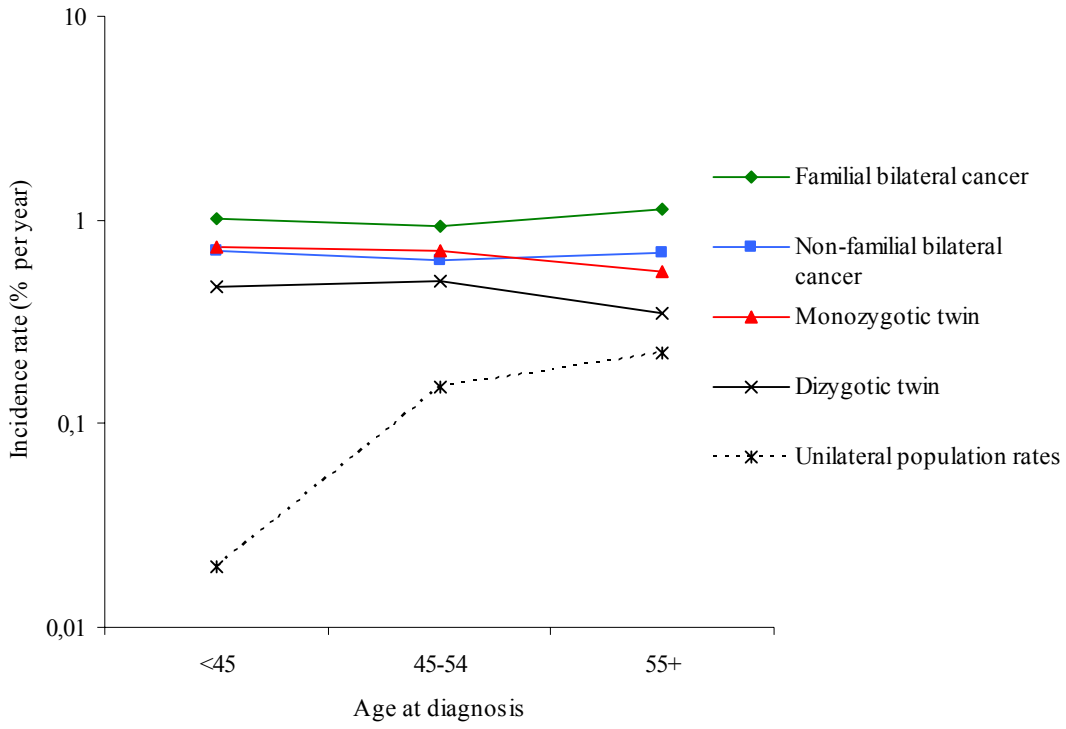
Familial breast cancer risk

There are to date several studies assessing the risk of familial breast cancer. These studies either estimate the effect of age or time since diagnosis. We have tried to asses the risk of familial breast disease taking age and time since diagnosis simultaneously into account. This can be achieved by studying risk of bilateral breast cancer and risk of breast cancer in twin sisters.

We used a large data set of Scandinavian twin sisters where at least one had a diagnosis of breast cancer. This design enabled convenient analyses of the onset of breast cancer in the twin sister. We identified a total of 2,499 twin pairs, 1221 from Sweden, 774 from Denmark and 504 from Finland, where at least one twin was diagnosed with breast cancer during the study period (Paper III). Of these 855 pairs were monozygotic and 1,644 were dizygotic. The concordance rate of breast cancer was 7.8% in monozygotic twin pairs and 5.2% in dizygotic pairs during a follow-up of 9,252 and 18,373 person-years, respectively. The breast cancer risk in twins was found to be little dependent of the

probands age at diagnosis, with monozygotic twins having higher risk than dizygotic twins (Figure 10). This finding is in sharp contrast to the age dependency seen in unilateral breast cancers and may suggest that the contribution from genetic factors are more important than environmental risk factors among relatives.

Figure 10. Incidence rate of breast cancer in women with previous breast cancer[α] or breast cancer affected 1st degree relatives[*β]. Swedish unilateral breast cancer rates added for comparison.



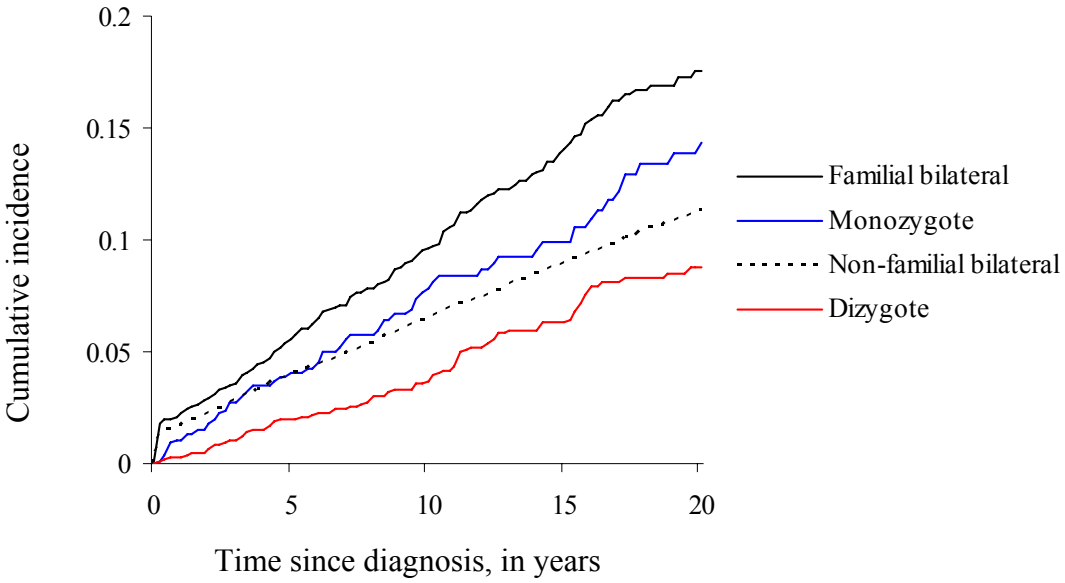
[α] Swedish women with a previous diagnosis of breast cancer 1970-2002. [*] Women with a breast cancer affected twin sister. Swedish cohort includes breast cancer cases diagnosed during 1958-2002. Danish cohort includes breast cancer cases diagnosed during 1943-1998. Finnish cohort includes breast cancer cases diagnosed during 1976-2005.[β] Age at diagnosis of first breast cancer for women with previous cancer and age at diagnosis of index twin sister.

From the Swedish Multi-Generation Register we identified a total of 93,448 women with breast cancer whose family links were known. For 87,338 women without a family history of breast cancer, 4,872 developed bilateral cancer after a follow-up of 650,742 person-years (Paper III). For 6,110 women with a family history, followed for 42,940 person-years, 443 had developed a bilateral cancer. The incidence of bilateral breast cancer is reportedly not modified by age and is approximately constant at 0.5% per year (35, 81).We observe similar to previous findings that the risk of bilateral breast cancer in our study is independent (constant) of both age and time since diagnosis (Figure 10 and Figure 11). Women with a family history of the disease experience a 50% higher risk of bilateral cancer compared to those without a family history but the pattern of risk, age

and time since diagnosis, was not dependant on family history. A constant risk might be consequence of an accumulation of a sufficient number of mutations (germline and somatic) at the point of the primary breast cancer, resulting in a high-risk group with an imminent risk of yet another cancer.

We modelled the risk for bilateral disease and the risk for disease in twin sister adjusted for follow-up time, period and country of diagnosis and attained age of woman at risk. In the comparison of the risk of bilateral breast cancer and the risk of disease in twin sisters there are several obvious similarities. We observed approximately 50% higher risk for familiar (IRR 1.52, 95% CI; 1.42-1.63) vs non-familial bilateral cancer (IRR 1.00, ref.) and similar increased risk for monozygotic twins (IRR 1.20, 95% CI; 0.96-1.46) compared to dizygotic twins (IRR 0.74, 95% CI; 0.61-0.90). Furthermore, the risk with increasing follow-up was fairly constant in all four categories

Figure 11. Nelson-Aalen estimates of primary breast cancer in twin sisters and of second primary breast cancer in women with and without an affected 1st degree relative with the disease.



Familial breast cancer prognosis

There is a wealth of information on conditions that are inherited and among those there is a clear association of inheritance of risk for several malignant conditions (73). So far it has been unclear to what extent, if at all, the outcome of a malignant condition and especially breast cancer is inherited. We therefore analyzed if the outcome of a female first degree relative with breast cancer predicts the outcome of her daughter or sister with the same disease.

We categorized the proband into categories of vital status 5 years after diagnosis and studied the 5 year survival proportion in their daughters or sisters. We present Kaplan-Meier plots of recently diagnosed (1991-) breast cancer patients (Figure 12). The 5-year cause specific survival proportion for daughters diagnosed 1991 onwards having mothers who died within 5 years was 87 percent (95 percent CI 82-91) compared to 91 percent (95 percent CI 89-93) for daughters with proband alive after 5 years, (log rank test, p=0.03) (Figure 12A). the 5-year cause specific survival proportion for a sister having an older sister who died of the disease within 5 years was 70 percent (95 percent CI 46-85) compared to 88 percent (95 percent CI 82-92) for sisters with proband alive after 5 years, (log rank test, p=0.01) (Figure 12B).

We present the 5-year breast cancer specific mortality for daughters and sisters by proband's prognosis (good, medium, poor) using a Cox proportional hazards model (Table 3). We estimated the 5-year cause specific mortality of the breast cancer patients by mother or sister proband separately. We present one model for all pairs, with adjustment for age at and calendar period of diagnosis including additional adjustment for age at first birth, parity, socioeconomic status and area of residence. The multivariable risk to die from breast cancer in the final model was 60% higher in daughters and sisters (HR 1.6, 95% CI 1.2-2.2) of a proband with a poor prognosis as compared to a proband with good prognosis. Analyzing sisters and daughters separately resulted in a similarly increased risk to die from breast cancer.

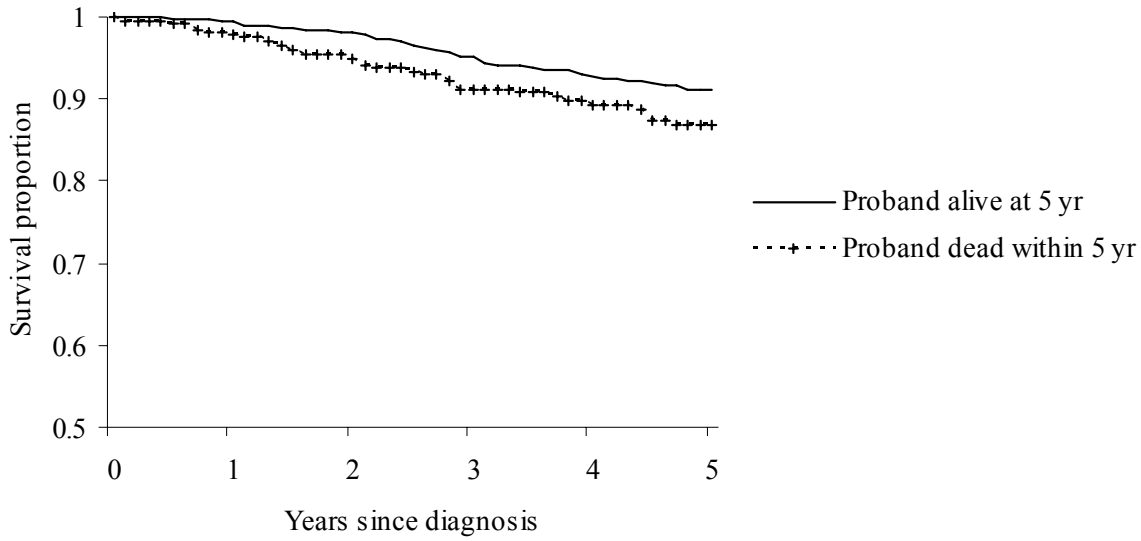
Table 3. Cox proportional hazards model of the 5-year cause specific mortality of 3,618 women with primary breast cancer by prognosis in proband (mother or older sister).

Proband prognosis**	Deaths	HR (95% CI)*†
Poor- (Tertile 1; <33%)	110	1.6 (1.2-2.2)
Medium-(Tertile 2; 33-66%)	106	1.4 (1.1-1.9)
Good-(Tertile 3; >67%)	70	1.0 ref.
Test for trend		p=0.002

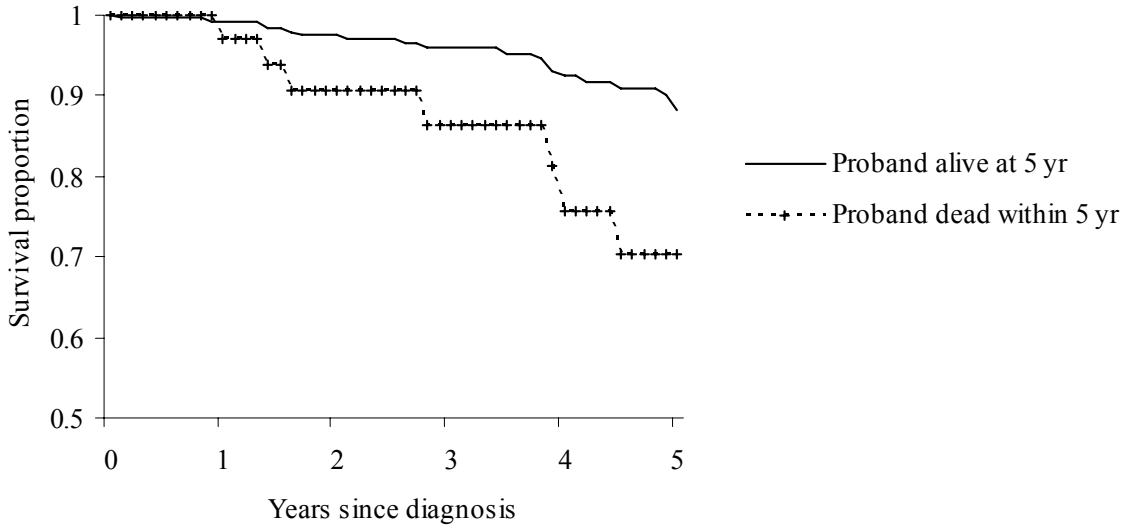
*HR-Hazard ratio, CI-Confidence intervals. **Proband's 5-year cause specific prognosis as defined by separated Cox proportional hazard model adjusted for proband's age and period of diagnosis.† Adjusted for age and period of diagnosis, parity, age at first birth, socioeconomic status and area of residence of the daughter or younger sister.

Figure 12. Kaplan-Meier estimates of breast cancer specific mortality of women diagnosed in 1991 onwards having a first-degree relative with breast cancer, stratified by proband's cause specific outcome. Panel A- 1778 daughter's with mother as proband. Panel B- 348 sister's with older sister as proband.

Panel A.



Panel B.



General discussion and discussion of findings

Methodological considerations

Validity

Internal validity is essential in a study to be able draw any conclusion from it. It is defined as the absence of any systematic error. There are two types of systematic errors, bias and confounding. Any form of bias will result in a distortion of an investigated association. There several types of biasis known of which some are important in register based cohort studies. They will be addressed below. Confounding on the other hand is a risk factor for the event and associated with the exposure. It may not be in the causal pathway between the exposure and the event, if it is in the causal pathway it is rather called an intermediate factor.

Bias

A diagnostic bias refers to a situation where the exposure, here unilateral cancer, influences the chance of being diagnosed. The opposite breast in women with unilateral cancer is probably one of the most heavily screened organs in the female body. As such there is some diagnostic bias in comparison to unilateral cancer, although a large proportion of unilateral cancers are screening detected by mammography (55, 130). The concern of any selection bias, that is a different chance of being recruited into the study seems less likely. Since reporting of a malignant condition to the Cancer Register is mandatory there is little likelihood of cancers not being reported to the Register. Each newly reported malignancy is assessed for histological origin and possibility of metastatic disease. In the event of a second primary malignancy this becomes very important, in order to avoid metastatic disease being misclassified as a new primary cancer. We have found no evidence of this being the case for bilateral breast cancer. Firstly, we have had personal discussions with the coding group at the Register describing the process of evaluating second primary malignancies. Secondly, the mortality pattern found in our studies for bilateral breast cancer is not that of metastatic disease. If such misclassification does occur it maybe differential in that it would include metastatic first primary breast cancer with subsequently very poor prognosis (131).

The definition of family history used in Paper III and IV is also unlikely to be subjected to any bias or misclassification since it is collected by the tax authorities and not dependent on personal reporting. Furthermore the information on cancer is also unlikely to be biased since reporting is madatory resulting in a high validity pedigree of breast cancer families are generated from 2 unbiased sources, namely the Cancer Register and the Multi-Generation Register. The twin definition of zygosity has been validated for all 3 twin registries and shown to classify more than 95% of pairs of twins correctly (119, 126, 127).

Loss to follow-up

Loss to follow-up refers to when, in this case women, can no longer be located. This is a potentially large problem in studies where the outcome is follow-up dependent. It may be very difficult to determine whether loss to follow-up is differential to any of the

subgroups and since it becomes very important to keep loss to follow-up to an absolute minimum. We observe in all of our 4 studies an emigration rate of less than 1%.

Length and lead time bias

In studies assessing risk of disease neither lead or length time bias becomes a problem. In survival studies they have to be addressed. Length time bias refers to how long a tumor might have existed in the body, that it its actual growth rate. At diagnosis the breast tumor is excised and it becomes virtually impossible to say how long it has been there. In a screening environment slower growing tumors will be detected at the screening interval, while faster growing tumors may surface as interval cancer. We do not have information on mode of detection and can not compensate for this.

Lead time bias refers to an artifact where the time of diagnosis of slowly progressing disease is made earlier in time. This increased time under observation may be do to improvements in the diagnostic work-up of the particular disease. Breast cancer in Sweden is now largely detected by mammography. With the introduction of service screening in the late 1980's many preclinical cancers became clinical and thus introduced an artificial lead time or increased survival time. The increasing incidence during 1970 to mid 80's for synchronous cancer observed in Paper II are most likely do to improvements in the clinical work up and the subsequent improvements in prognosis for synchronous cancer may reflect this phenomenon.

Confounding

Confounding leads to biased estimates, however if confounding is known and measured, it can be adjusted for in the analysis. A confounder should possess three basic qualities; 1. It should be associated with the exposure, 2. It should be associated with the outcome and 3. The confounder may not be in the causal pathway between the exposure and the outcome. In Paper I and II we have limited information on the study participants allowing for confounders to bias the results. In the analysis in both papers comparing the crude unadjusted results to the multivariate models where we adjust for the known covariates there was an effect on incidence and prognosis trends. Suggesting that age, calendar period and time since diagnosis are important confounders for the risk and prognosis of bilateral disease. The validation cohort of paper II holds additional information on stage and estrogen receptor status etc.. Adjustment for stage in the survival analysis exaggerated the association of risk to die from bilateral disease by time since diagnosis of first cancer. This suggests that stage is a negative confounder for bilateral disease, where the risk to die from the disease is greater than suggested by stage alone.

Precision, random error and power

Random error occurs by chance alone and it leads to false associations between the exposure and the outcome. It can occurs by any number of sources, such as measurement error caused by erroneously registered dates, type of cancer (ICD code), laterality etc. (131). Therefore chance can never be excluded as a source of an observed association (132), but with statistical method the role of chance as an explanation can be estimated.

In this thesis, the influence of random error or chance was estimated through calculations of point estimates with p-values and confidence intervals around these estimates. The confidence level was set to 95%, which means that with a 95% probability the true estimate lies within those limits. By the same reasoning, with a probability of 1 in 20 the true estimate lies outside of those limits. With increasing sample size the uncertainty of an estimate decreases and the confidence limits around the estimate narrows. Power refers to the statistical ability to find a difference between study groups according to the Null hypothesis. An estimation of the probability to find such a difference if it exists is made prior to embarking on the study. Usually a power of 80% is accepted, which means the study has a .8 probability to find a difference if one exists or a 20% chance to miss it.

External validity

External validity refers to the ability to generalize the finding of a study to other populations. Can our studies in Sweden, for example, have any bearing on the risk and prognosis of breast cancer in the United States? The ability to generalize findings to other populations has several prerequisites. Firstly, the study must have a high internal validity. Secondly, the external validity is dependant on a number of factors such as age distributions, prevalence of exposures and the occurrence or absence of exposures in the population to be compared with. For example, we have a source population that under the better part of the study period was subject to mammography screening, resulting in probably smaller tumors with better survival. If the population one wishes to generalize the finding to do not have a screening program this will make it difficult to compare incidence and survival patterns of breast cancer.

Study design

Cohort studies (Paper I-IV) allows generally for the study of a few exposures with multiple outcomes. The study design is usually very time consuming and expensive. In Sweden we have the advantage of already assembled cohorts of individuals that can easily and at low cost be accessed. The main drawback is the limited amount of exposure information available, but instead we have the advantage of very large population-based samples.

In the design of a cohort study there is an issue of choosing comparison group. The ideal comparison group to women with bilateral breast cancer in a study looking for risk factors for disease might instead of women with unilateral cancer be healthy women. Since the baseline risk of disease for those women is considerably lower. In contrast, when studying the outcome of bilateral cancer the comparison to women with unilateral cancer is more obvious.

Bilateral breast cancer

Synchronous bilateral breast cancer

The incidence pattern of synchronous cancer is similar to that of unilateral disease though without any notable trends in recent decades. Synchronous breast cancer has an incidence

far higher than what could be expected by chance alone. The incidence of unilateral breast cancer between ages 50-59 years is 200 per 100,000 person-years, which corresponds to a risk of 200 cases in 200,000 breasts in a year, or a probability of .001 per breast. So the probability that both breasts experience a cancer within 3 months of each other would be .00025 x .00025= .0000000625. The incidence of synchronous breast cancer is approximately equal to a risk of 2 per 100,000 person-years or 0.5 per 100,000 persons per 3 months. This constitutes a probability of 0.000005 which is a factor approximately 100 fold greater than would be expected if the cancers occurred at random. This observation would suggest that synchronous breast cancer occurs in a genetically susceptible subgroup of women. However the lack of an early age of onset(133) as seen for women with mutations in BRCA1 and BRCA2 genes (134) is inconsistent with a germline mutation being a significant etiological factor in synchronous breast cancer. By contrast, this excess risk may be attributable to an accumulation of exposures to environmental carcinogens in this subgroup of women which would also be consistent with the similarities in age-dependence of risk for bilateral synchronous and unilateral breast cancers (Figure 7).

The gradual increase in the incidence of synchronous disease during the 1970s coincides with the introduction of routine and bilateral mammography as part of the diagnostic workup in women with unilateral cancer (135). Such workup may entail that some preclinical bilateral cancers becomes detected early and classified as synchronous disease (32) – perhaps in an earlier and more favourable stage (136) – rather than diagnosed later as metachronous disease. A recent study employing MRI of the opposite breast has demonstrated how intensive clinical workup can increase detection of small tumors (137). Synchronous bilateral disease before age 50 years approximately doubles the mortality rate – as one would expect if forces of mortality from the two primary tumors act independently – whilst after age 50 years the excess mortality compared with unilateral disease is much smaller (Paper II). It is difficult to explain the lack of additive mortality at older ages.

Metachronous bilateral cancer

We found profound differences in the incidence trends and prognostic outlook between synchronous and metachronous bilateral breast cancer diagnosed at different ages. The overall incidence rate of metachronous bilateral breast cancer in Paper I and II is compatible with that reported by other investigations, particularly when differences in sample size, age distribution, and follow-up time are taken into account (5, 31, 35, 36). Among women diagnosed with a unilateral cancer, the incidence rate of metachronous bilateral cancer was substantially higher than that of a first primary breast cancer among previously healthy women (Figure 7). Moreover, the occurrence of metachronous cancer was age-dependent in a manner markedly different from that of unilateral or synchronous bilateral disease. Specifically, the incidence was higher before 50 years of age (Figure 7). Similar incidence patterns for metachronous lesions have been reported in some other studies (31, 36, 78). Our data provide strong evidence that, as age advances after a diagnosis of a first breast cancer, bilateral breast cancer does not exhibit the increase in incidence familiar to unilateral cancer.

The absolute risk for an individual being diagnosed with a second breast cancer in Paper I in the years following her diagnosis illustrate a particularly high incidence of metachronous breast cancer in the first ten years after diagnosis among women younger than 45 years. In the first 20 years following a diagnosis of primary breast cancer, the incidence of metachronous bilateral cancer decreased from about 0.8 to 0.4% per person-years in patients diagnosed with the first breast cancer before age 45 years, whilst the incidence remained stable at 0.5 – 0.6% per person-years among those who were older than 45 years at diagnosis. After 30 years of follow-up, the cumulative risk of metachronous bilateral breast cancer approached 15% regardless of age at first primary breast cancer. The risk of metachronous breast cancer is comparatively low, in our series between 0.4 – 0.8 % annually depending on age at and time since diagnosis of the first cancer. There is an important connection between synchronous and metachronous cancers that is determined by the clinical work-up. Improved detection is of course more likely to diagnose a bilateral cancer earlier than later, therefore some of the increase in synchronous cancers seen during the study period should be reflected by a decrease in metachronous cancers. However this shift from earlier to later diagnosis is difficult to measure, especially in an environment of adjuvant treatment that is likely to reduce the incidence of bilateral cancer. As increasing number of young women are being successfully treated they will live long enough to develop a second cancer. For some patients prophylactic contralateral mastectomy could be carefully considered. However, with regular radiological surveillance of the contralateral breast second tumors are likely to be detected at an early stage.

The incidence of metachronous cancer in Paper II decreased by about 30% since the early 1980s most likely due to increasing use of adjuvant therapy. This effect has been demonstrated in several randomized clinical trials (47, 51), but has not previously been observed on a population level in Sweden. This finding is of course very encouraging for women diagnosed with unilateral breast cancer. Women who developed bilateral cancer within 5 years and before age 50 were 3.9 times (95% CI 3.5-4.5) more likely to die from breast cancer than women with unilateral cancer (Figure 9). Women with a bilateral cancer diagnosed more than 10 years after the first cancer had a prognosis similar to that of a unilateral breast cancer. Adjuvant chemotherapy of primary cancer is a predictor of poor survival after diagnosis of early metachronous cancers, while adjuvant chemotherapy following the second cancer is not associated with a poor prognosis (Table 2). Adjuvant chemotherapy therapy seems to have a dual effect on metachronous cancer; it reduces the risk, while it at the same time seems to worsen the prognosis. It should be pointed out that the proportion of women that benefited the most from adjuvant treatment, namely those that did not develop bilateral cancer are not included in the analysis in Table 2.

Familial breast cancer

The risk of breast cancer in the opposite breast and in twin sisters in Paper III show a remarkably similar onset of disease and risk pattern, yet a very different pattern from the risk of breast cancer in the general population. The high and constant risk of disease suggests that these women have already aggregated genetic prerequisites for breast cancer. The lack of even further elevated risks in monozygotic twin sisters and in women

with familial bilateral cancer suggests some form of risk saturation. Our results could also be interpreted that the baseline risk of breast cancer in the population is so high that genetic factors only marginally further increase the risk. Finally, the presented findings may have implications for counseling of women with breast cancer since family history of the disease increases the already high risk of bilateral disease further. Furthermore the finding of possible risk saturation does shed light on the carcinogenesis of breast malignancy.

We conclude that information about the outcome of breast cancer in Paper IV among affected first degree relatives conveys prognostic information relevant to women with newly diagnosed breast cancer. This novel observation might become relevant for clinical management provided that the post prognostic information can be shown to be independent of that from established predictors of outcome. Further research into the likely genetic determinants of inherited breast cancer prognosis might also provide new biologic insight.

Clinical perspective

Young women who develop breast cancer are at a considerably high risk to develop yet one more breast cancer in the opposite breast 10 years following initial diagnosis (Paper I). There does not seem to be any time after diagnosis of the first cancer when she assumes the same risk as the background population. If the woman actually does develop a bilateral cancer, her risk to die is extremely dependant on her age at diagnosis, time since first cancer and also on the type of adjuvant therapy she received for the initial cancer (Paper II). What are the possible implications in the clinical setting? The contralateral breast is probably the most intensely screened organ in the female body and thus tumors that arise would be small and with a favorable stage, still prognosis is poor. The increased risk for disease per se does not seem to warrant any prophylactic measures, such as prophylactic surgery since the life time risk is below 20%. If the bilateral breast cancer prognosis would be equal to unilateral cancer the previous argument would hold, but since it does not seem to be true the decision for prophylactic measures in certain subgroups may have to be revised. Regardless of any prophylactic measures, women who develop bilateral breast cancer may warrant more aggressive therapy than what is given by known prognosticators (Paper II).

We observe in Paper II that the risk of metachronous disease decreased by 30% during that last 30 years. This is an extraordinary finding for women with breast cancer, the net result being a considerable number of women spared of another malignancy. The most reasonable interpretation is the increased use of adjuvant therapy, which emphasizes that what ever we are doing on the national level is having a major impact.

Women who seek clinical counseling for breast cancer are interested of receiving an individual risk estimate of breast cancer (75, 76). It is not unlikely that implicit in their wish is to avoid a deadly disease, which nowadays has a good prognosis with an estimated 85% 5-year survival (85). Therefore it is even more important to identify not only who is at risk of breast cancer, but who is at risk to die from the disease. In the clinical counseling setting we have tried to answer 2 questions. The first is at what age

after the age of a 1st degree relatives diagnosis with breast cancer a women is at risk of the disease. The second question is if the outcome of the 1st degree relative predicts death in women diagnosed with breast cancer. Our findings in Paper III suggest that having a first degree relative with breast cancer puts you at a high risk at least from that age onwards. At what age to start breast cancer screening for this subgroup is difficult to say from our results. In paper IV we observe that prognosis in 1st degree family member predict outcome in their relatives. The implications are two-fold. The first being that a simple question of whether a woman's mother or sister died of breast cancer predict outcome. The second is that there is evidence to suggest that genetic markers for prognosis exist. Identifying unbiased prognosticators does seem feasible.

Final remarks and future research

Bilateral breast cancer

Our results suggest that metachronous breast cancers diagnosed in premenopausal women might be due to genetic susceptibility, while synchronous breast cancer may to a higher degree be associated with environmental factors. We feel that association studies aiming at identifying polymorphisms that differ between both healthy women and those with uni- and bilateral breast cancer would be a useful approach to identify genetically susceptible subgroups. Further research into the complex behaviour of bilateral breast cancer may provide important new insight, biologic and clinical.

Although adjuvant therapy is a cornerstone in the management of breast cancer, most women do not benefit from these therapies, but rather only experience side effects (59). Thus, selecting patients into groups that are likely to respond to specific adjuvant therapies has become one of the most important challenges in breast cancer therapeutics. Since we recently discovered that the prognosis is especially poor for women who develop a bilateral cancer within 5 years of first cancer and were given adjuvant chemotherapy, it would be very interesting to find out why. In our data there is little to suggest that the observed pattern originates from metastases from the first tumor, but rather from second primary cancers with a poor prognosis. Thus, in accordance with previous reports, it seems that tumors presenting during adjuvant therapy have a poor prognosis due to therapy resistance (69). Since systemic chemotherapy is more often given to younger women, whom when diagnosed with bilateral breast cancer have the worst prognosis, it further supports the idea of tumor selection due to adjuvant therapy. We would like to further investigate if a particularly poor prognosis is seen in those treated with systemic chemotherapy as compared to those treated with hormonal therapy using more detailed information from medical records and if it is possible to identify a molecular resistance pattern in breast cancers that develop during adjuvant therapy. If such a resistance pattern does exist it may be feasible to apply such a pattern to all women with breast cancer to better select those that will benefit from treatment.

Familial breast cancer

We have found that information about the outcome of breast cancer among affected first degree relatives conveys prognostic information relevant to women with newly diagnosed breast cancer. This observation might become relevant for clinical management provided that the post prognostic information can be shown to be independent of that from established predictors of outcome. An obvious next step will be to investigate if familial breast cancer outcome is an independent prognosticator. Further research into the likely genetic determinants of inherited breast cancer prognosis might also provide new biologic insight. Similar studies of other cancer sites should also be a high priority. We plan to study the correlation in genetic markers (single nucleotide polymorphisms) and gene copy aberrations in tumors between sisters to investigate if the inheritance of prognosis is mediated by tumour characteristics. Since it is also yet unclear what is actually inherited, familial studies using twins would be of interest to estimate ‘the heritability of prognosis’.

Conclusions

The risk of bilateral breast cancer is considerable at about 0.5% per year in women with unilateral disease.

Young age at first breast cancer almost doubles the risk of a second cancer.

Women with unilateral breast cancer are at a constant lifelong risk of one more cancer, but the absolute risk does not seem to warrant prophylactic measures.

Women with bilateral breast cancer have a poor survival. Predictors of a poor outcome include young age at first cancer, a second diagnosis within 5 years and those treated with adjuvant chemotherapy for the first cancer.

The overall risk of bilateral breast cancer and breast cancer in twin sister is very different from the risk of breast cancer in the general female population. The risk patterns in these high risk groups include a high age-independent and constant risk.

There is evidence that not only risk of breast cancer, but also prognosis might be inherited.

If a first degree relative died of breast cancer within 5-years of diagnosis, it increases the risk of her relative to have a poor outcome.

Svensk sammanfattning

Målet med denna avhandling var att öka förståelsen kring risk och prognos i bröstcancer genom att studera högrisk grupper av kvinnor med familjär och dubbelsidig bröstcancer.

Information från Svenska Cancer Registret, Flergenerations Registret och Dödsorsaks Registret har använts i artikel I-III för att identifiera kvinnor med dubbelsidig bröstcancer och för att studera risk och prognos i sjukdomen. Förekomsten av synkron bröstcancer (< 3 månader från 1:a cancern) ökade med stigande ålder och med 40% under 1970-talet, medan förekomsten av metakron cancer (≥ 3 månader från 1:a cancern) minskade med ålder och med 30% sedan tidigt på 1980-talet sannolikt pga ökande användning av adjuvant behandling. Under de första 20 åren efter den 1:a bröstcancer diagnosen minskar risken för metakron cancer från 0.8% per år till 0.4% per år hos kvinnor <45 år medan risken är oförändrad på 0.5-0.6% per år bland kvinnor >45 år vid diagnos. Kvinnor med bilateral cancer inom 5 år och före 50 års ålder hade 3.9 gånger (95% CI 3.5-4.5) större risk att dö pga bröstcancer jämfört med kvinnor med en cancer. Kvinnor med bilateral cancer diagnostiserad mer än 10 år efter 1:a cancern hade samma prognos som kvinnor med en cancer. Adjuvant kemoterapi vid 1:a diagnos är en prediktor för dålig överlevnad i tidig metakron cancer.

I artikel III jämför vi risken för familjär och icke familjär bilateral sjukdom med risken för bröstcancer hos tvillingsystrar i Sverige, Danmark och Finland. Vi har observerat risker som är upp till 5 till 7 gånger större i absoluta mått och med ett helt annat åldersmönster när vi jämför risken för sjukdom i det med motsatta bröstet och hos tvillingar med förekomsten i den kvinnliga befolkningen. Risken för cancer hos den friska tvillingen och i det motsatta bröstet var inte relaterad till ålder eller tid sen 1:a cancern Den relativa risken för familjär bilateral cancer var 52% högre (IRR 1.52, 95%CI; 1.42-1.63) och den relativa risken hos den dizygota tvillingsystern var 26% lägre (IRR 0.74 95%CI; 0.61-0.90) jämfört med risken för icke familjär bilateral cancer.

I artikel IV analyserar vi om bröstcancerprognos är ärftlig genom att använda ett länkat dataset från Svenska Cancer Registret och Flergenerations Registret. Vi identifierade 3,618 mamma-dotter och syster par med bröstcancer och klassificerade bröstcancer specifik 5-års överlevnad i tertiler bland mammor och den äldsta systern som dålig, medium och bra. Efter justering av potentiella confounders hade döttrar och yngre systrar med släktingar med dålig prognos en 60% högre 5 års mortalitet jämfört med släktingar med god prognos (relativ risk 1.6; 95 %CI 1.2-2.2; p för trend 0.002).

Sammanfattningsvis så är risken för familjär bröstcancer hög och skiljer sig i åldersmönster från risken hos bakgrundsbefolkningen. Risken för bilateral cancer är också hög och prognosen dålig, samtidigt som både risk och prognos är relaterade till användningen av adjuvant behandling. Avslutningsvis så finns det tecken på att bröstcancerprognos är ärftlig.

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