Department of Medicine
Clinical Epidemiology Unit (KEP)
Karolinska Institutet, Stockholm, Sweden

REPRODUCTIVE FACTORS WITH RESPECT TO BREAST CANCER RISK AND BREAST CANCER SURVIVAL

Mohammadhossein Hajiebrahimi

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Reproductive factors with respect to breast cancer risk and breast cancer survival
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By

Mohammadhossein Hajiebrahimi

Principal Supervisor:
Shahram Bahmanyar
Karolinska Institutet
Department of Medicine
Division of clinical Epidemiology Unit (KEP)

Co-supervisor(s):
Sven Cnattingius
Karolinska Institutet
Department of Medicine
Division of clinical Epidemiology Unit (KEP)

Mats Lambe
Karolinska Institutet
Department of Medical Epidemiology and statistics (MEB)

Anastasia Nyman Iliadou
Karolinska Institutet
Department of Medical Epidemiology and statistics (MEB)

Opponent:
Prof. Jonas Manjer
University of Lund
Department of surgery

Examination Board:
Ass. Prof. Lisa Ryden
University of Lund
Department of surgery

Prof. Kamila Czene
Karolinska Institutet
Department of Medical Epidemiology and statistics (MEB)

Ass. Prof. Jana de Boniface
Karolinska Institutet
Department of Molecular Medicine and Surgery

Dedication

All women who have suffered and, in the worst case, died from breast cancer

ABSTRACT

Aims: The primary aim of this thesis was to examine the potential relationship between indirect markers of exposure to hormones during pregnancy and the risk of and survival from breast cancer, with special emphasis on young patients. Our specific objectives were as follows: to determine whether the association between placental weight and offspring size, on the one hand, and maternal mortality from breast cancer, on the other, are influenced by tumor characteristics; to examine the association between birth weight and risk of breast cancer in the female member of opposite-sexed twins; and to investigate whether familial factors influence previously reported association between reproductive factors and risk of breast cancer.

Methods: Based on the Swedish Quality Register of Breast Cancer, two different cohort studies were designed in the Stockholm-Gotland and Uppsala-Örebro regions, where records on characteristics of breast cancer have been collected since 1992. The first cohort was restricted to women who had a pregnancy between 1982 and 1989, and subsequently developed breast cancer. The cohort included 1,067 subjects and 180 deaths, and was conducted to investigate if placental weight is associated with maternal risk of dying from breast cancer, taking tumor characteristics into account. In the second study, we studied the possible association between birth weight and maternal risk of death from breast cancer, also taking tumor characteristics into account. We included 6,019 women who had a pregnancy between 1973 and 2008 and subsequently developed breast cancer, of whom 1017 died from the disease.

Two case-control studies were also performed. In a nested case-control study, involving the female members of opposite sexed twin pairs, 543 cases and 2715 controls were included to investigate the potential association between offspring birth weight and risk of breast cancer, as well as a possible modifying effect of birth weight of the male twin sibling. Information on the twins (including birth weight, birth height, head circumference and gestational age of the females, and birth weight of the male co-twin) was extracted from the Swedish Twins Register and data on women diagnosed with breast cancer from the Swedish Cancer Register.

A second case-control study examined the potential modifying effect of familial factors on the association between reproductive factors and the risk of breast cancer. All women who delivered between 1973 and 2010 and had a full sister were selected as the study population, using the Swedish Medical Birth Register. Information on breast cancer was obtained from the Swedish Cancer Register and sisters were identified using the Swedish Multi-Generation

Register. The cases examined included all parous women diagnosed with breast cancer between 1973 and 2010 who were 50 years old or younger and had at least one sister who also gave birth during this same period. The two control groups were sister controls (including the sister without breast cancer and closest in age to the case) and population controls (all parous women without breast cancer with at least a full sister except those in the sisters control group). In total, 8,349 cases, 8,349 sister controls, and 1,053,688 population controls were used.

Results: Our findings indicate that the association between higher placental weight in connection with the most recent pregnancy and maternal risk of mortality from premenopausal breast cancer is dependent on the receptor status of the tumor. A positive association was more pronounced in the case of ER-/PR- tumors, but we did not find a dose–response association. Birth weight demonstrated no association with maternal mortality from premenopausal breast cancer, even in analyses stratified by the time that elapsed between pregnancy and cancer diagnosis, tumor stage, and receptor status. There was an inverse association between birth-weight-for-gestational age and mortality from premenopausal breast cancer among uniparous women. The nested case-control study of opposite-sexed twins did not reveal any statistically significant association between birth weight and risk of breast cancer. Furthermore, we observed no associations between other birth characteristics, including co-twin birth weight, and the risk of developing pre- or postmenopausal breast cancer.

Our last study provided some evidence that the association between reproductive factors and maternal risk of breast cancer or between maternal factors and maternal risk of breast cancer may differ when using population or sister controls. We found that parity exhibited an inverse association to premenopausal breast cancer using population controls and was a risk factor using sister controls, suggesting a gene-environment interaction. Very preterm delivery ($\leq$31 weeks) was associated with a higher breast cancer risk using sister controls than when population controls were used, also suggesting a gene-environment interaction.

Conclusions: We found some, but no strong evidence in support of the hypothesis that higher hormone levels during pregnancy are associated with mortality from premenopausal breast cancer. The hypothesis was supported when placental weight was employed as indirect indicator of estrogen levels during pregnancy, although birth weight showed no such association. The more pronounced effect of placental weight among ER-/PR- tumors suggests that premenopausal hormonal exposure might exert a greater impact on such tumors. The association between parity and risk of premenopausal breast cancer was modified by a gene-

environment interaction, as was the association between gestational age and the risk of breast cancer.

Keywords: Breast cancer, Premenopausal, Postmenopausal, Placental weight, Birth size, Tumor characteristics, Estrogen Receptor, Progesterone Receptor, Twin, Opposite-sex, Sister control, Population control

LIST OF SCIENTIFIC PAPERS

This thesis was based on the following articles:

I. **Hajiebrahimi MH**, Bahmanyar S, Lambe M, Adolfsson J, Fornander T, Wärnberg F, Cnattingius S. Placental weight and mortality in premenopausal breast cancer by tumor characteristics. Breast Cancer Res Treat 2013 Jan; 137(1):297-305.

II. **Hajiebrahimi MH,** Cnattingius S, Lambe M, Hsieh C-C, Ahlgren J, Adolfsson J, Bahmanyar S. Birth size in the most recent pregnancy and maternal mortality in premenopausal breast cancer by tumor characteristics. Breast Cancer Res Treat 2014 Jun; 145(2):471-80.

III. **Hajiebrahimi MH**, Bahmanyar S, Öberg S, Nyman Iliadou A, Cnattingius S. Breast cancer risk in opposite-sexed twins: influence of birth weight and co-twins birth weight. J Natl Cancer Inst. 2013 Dec 4; 105(23):1833-6.

IV. **Hajiebrahimi MH,** Cnattingius S, Lambe M, Bahmanyar S. Pregnancy history and risk of breast cancer - a nested case control study on sisters discordant for breast cancer. In manuscript.

CONTENTS

List of Abbreviations

AGA	Appropriate for Gestational Age
BMI	Body-Mass Index
BW/GA	Birth Weight for Gestational Age
CI	Confidence Interval
DZ	Dizygotic
ER	Estrogen Receptor
GA	Gestational Age
HR	Hazard Ratio
HER2	Human Epidermal Growth Factor Receptor-2
ICD	International Classification of Disease
IGF1	Insulin-like Growth Factor-1
LGA	Large for Gestational Age
LMP	Last Menstrual Period
MFR	Medical Birth Register
MGR	Multi-Generation Register
MZ	Monozygotic
OR	Odds Ratio
PI	Ponderal Index
PR	Progesterone Receptor
RCT	Randomized Clinical Trial
SCR	Swedish Cancer Register
SCDR	Swedish Cause of Death Register
SGA	Small for Gestational Age
SQRBC	Swedish Quality Register of Breast Cancer
STR	Swedish Twins Register
SHBG	Sex-Hormone Binding Globulin
TDLU	Terminal Duct Lobular Units
TNBC	Triple-Negative Breast Cancer
VLGA	Very Large for Gestational Age
VSGA	Very Small for Gestational Age

1. Introduction

Breast cancer is the most common form of cancer among women worldwide and its incidence is increasing in all countries, being highest in high income countries (1). In Sweden, for instance, one in every eight women is diagnosed with breast cancer during her lifetime (2). Despite the declining mortality from breast cancer in high-income countries in recent decades, this form of cancer still kills women more than any other form in all nations (3).

Estrogens and reproductive factors associated with exposure to estrogen e.g., low parity, early age at menarche, late age at menopause, and late age at the time of first pregnancy, are well-known risk factors for breast cancer. During the course of life, women are exposed to different levels of estrogen, especially high levels during their fetal life and when they become pregnant. Thus, exposure during these latter periods may be particularly important for the development of breast cancer. The impact of reproductive factors on the risk of breast cancer has been examined in many studies and some researchers propose that these factors may also play a role in breast cancer mortality.

Tumor characteristics, including stage, expression of hormone receptors and histopathology, are prognostic factors for the outcome of breast cancer, including mortality. Moreover, the expression of a group of hormone receptors may provide a better indicator than considering these receptors individually. Thus, at the twelfth St Gallen International Breast Cancer Conference an expert panel, introduced a new method for classification of breast cancer for therapeutic purposes based on a combination of the estrogen receptor (ER), Progesterone receptor (PR), and human epidermal growth factor-2 (HER2) (4). It seems likely that reproductive factors exert different impacts on the prognosis for breast tumors with different characteristics.

The primary aim of the present thesis was to examine associations between indirect markers of antenatal exposure to hormones and the risk of and survival from breast cancer. Taking tumor characteristics into account, associations between pregnancy and offspring characteristics and maternal mortality from breast cancer were focused on in two investigations. In another study, the possible relationship of birth characteristics and breast cancer risk in the female member of opposite-sexed twin pairs was explored. Finally, the possible influence of familial factors on the relationship between reproductive factors and the risk of breast cancer was examined.

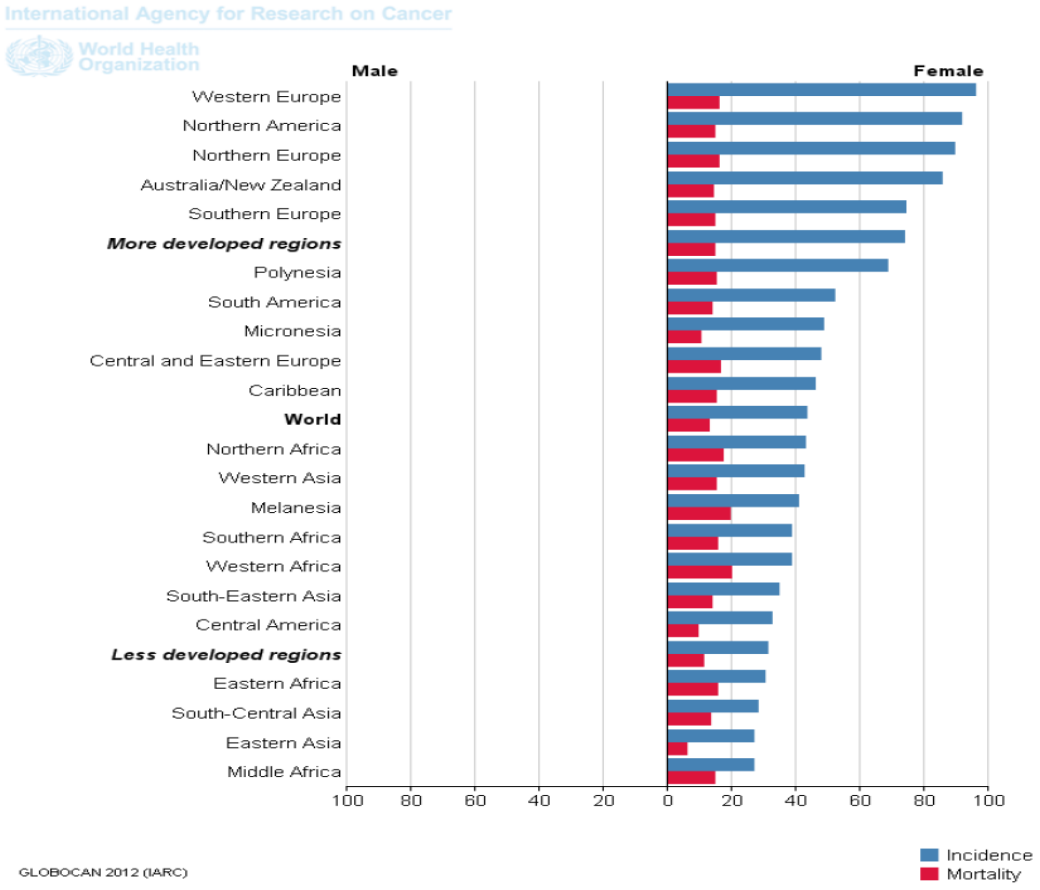
2. Background

2.1 Epidemiology

2.1.1 Incidence

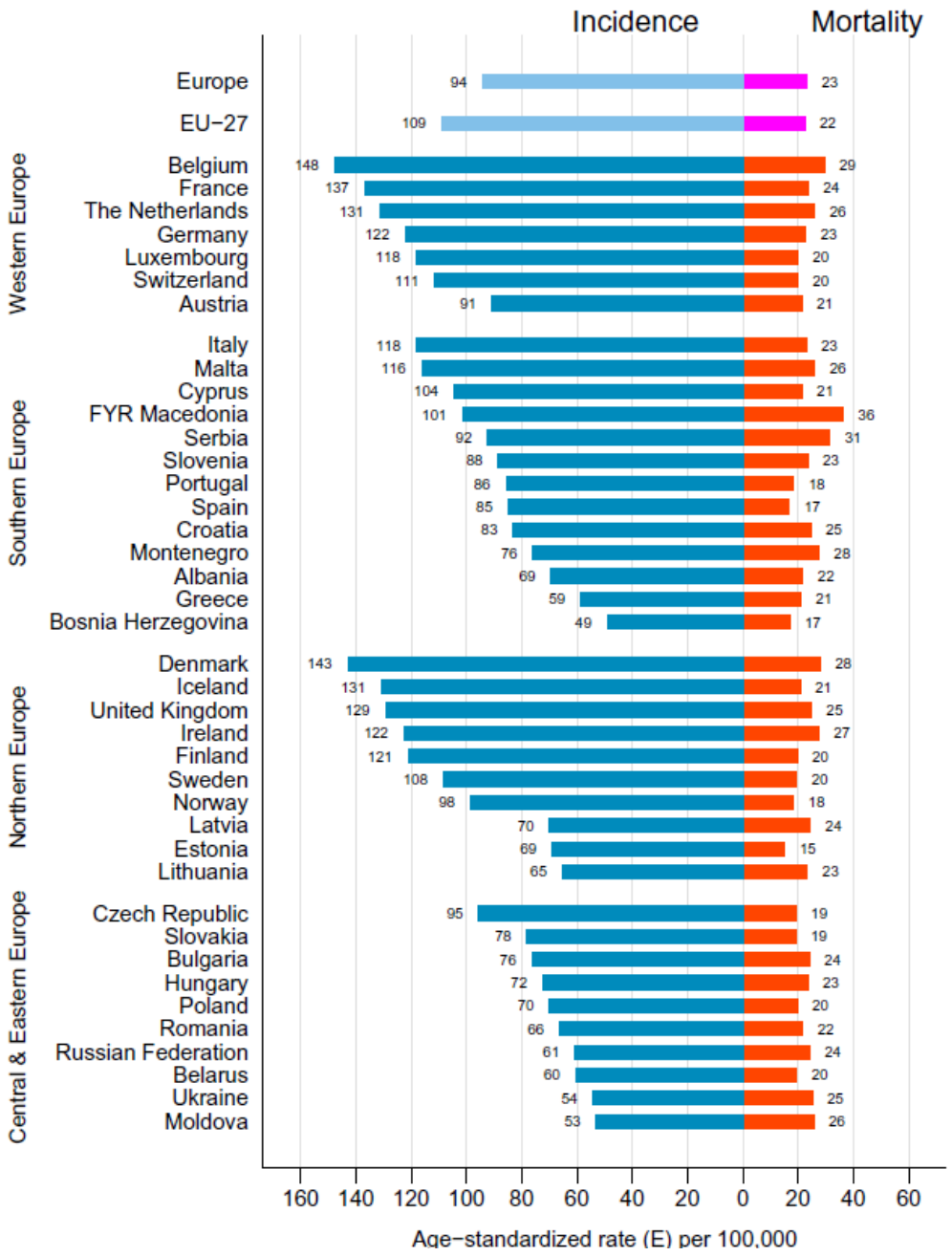
In 2012, breast cancer accounted for 25% of newly diagnosed cancers among women around the world (1), with the highest incidences in high-income countries (Figure 1) (5-7). In this same year, the age-standardized incidence of breast cancer in Sweden was approximately 108 per 100,000 population (Figure 2) (8), comprising 30% of all female cancers (Figure 3)(2) and afflicting approximately 1 of every 8 Swedish women during their lifetime.

Figure 1: Estimated age-standardized rates of the incidence and mortality from breast cancer (per 100,000 populations) in different regions in 2012



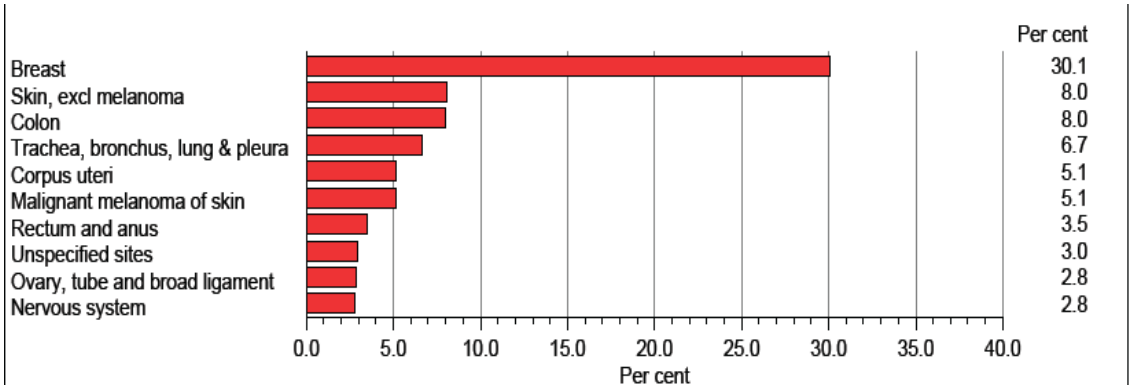
(Taken from Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC, CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 04.04.2014, with

Figure 2: Age-standardized incidence of and mortality from breast cancer per 100,000 population in Europe in 2012



(Taken from Ferlay et al. European Journal of Cancer, 2013, with permission from Elsevier).

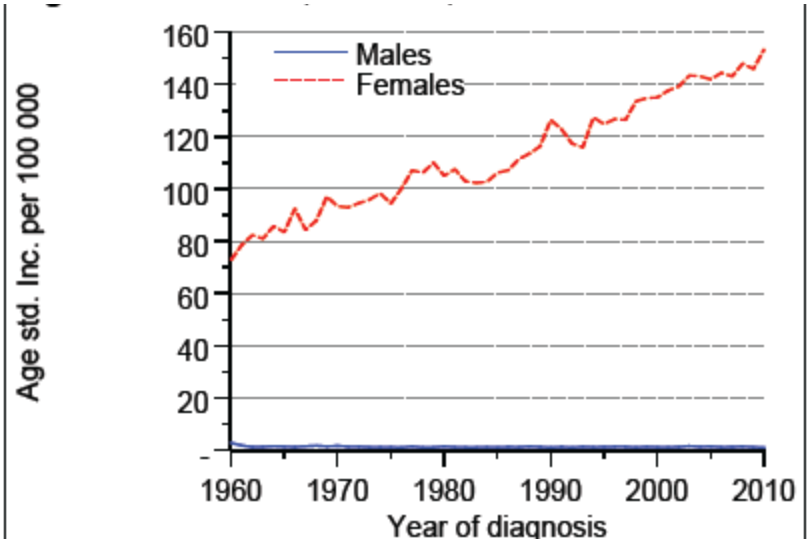
Figure 3: The relative frequencies of different form of cancer in Sweden in 2010



(Socialstyrelsen - The National Board of Health and Welfare, Official Statistics of Sweden, Statistics – Health and Medical Care, Cancer Incidence in Sweden 2010)

The annual increase in breast cancer incidence in Sweden has been approximately 1.3% during the past 20 years (Figure 4)(2) .

Figure 4: Overall cancer incidence in Sweden since 1960



(Socialstyrelsen - The National Board of Health and Welfare, Official Statistics of Sweden, Statistics – Health and Medical Care, Cancer Incidence in Sweden 2010)

2.1.2 Mortality

In 2012, more than 14% of all cancer deaths in low-income countries were due to breast cancer (1). In spite of the fact that the relative rate of mortality is lower in high-income countries, the higher incidence in these countries (90/100,000 women) than in low-income countries (30/100,000 women) means that the overall mortality from breast cancer is almost equal (15/100,000 women) (3). In Europe, the risk of breast cancer mortality varies two-fold between countries (8). For example, the age-standardized mortality from breast cancer are 29 and 28 per 100,000 population in Belgium and Denmark, respectively, but only 15 and 17 per 100,000 in Estonia and Spain. In Sweden, the corresponding rate is 20 per 100,000 (Figure 2)(8), and the annual reduction during the last four decades is around 1% (9).

2.2 Risk factors for breast cancer

The incidence of breast cancer increases with age. Although one possible definition of aging is "*the accumulation of cell mutations and tissue damage that leads to disease*", aging does not itself induce all such changes (10), but is rather thought to reflect of the occurrence different life-events. Thus, the risk of breast cancer may be influenced by genetic changes, exposures during prenatal and early life, reproductive factors and late-life exposures such as those associated with hormone replacement therapy and menopause. For example, in an older woman a low-grade breast cancer with good-prognosis in terms of progression might be caused by a lack of DNA genomic material on the long arm of chromosome 16 (11). Thus, the impact of risk factors such as age at menarche, the time of first pregnancy and of first full-term pregnancy that changes with age (12, 13) may be due to long-term exposure to, e.g., estrogens, rather than to increasing age itself. Even though the impact of certain risk factors for breast cancer such as a high body-mass index (BMI) increases with age, this might reflect physiological changes rather than simply increasing age.

2.2.1 Familial factors

2.2.1.1 BRCA1 and *BRCA2*

Mutations in genes such as *BRCA1* and *BRCA2* appear to be responsible for less than 10% of breast cancers (14, 15). Mutations in *BRCA1*, a tumor suppressor gene identified in 1990 and located on chromosome arm 17q (16), are rare in the general population (Table 1), but carried by approximately 5-10% of women diagnosed with breast cancer (17). Such mutations are also linked to an enhanced risk of ovary cancer.

Women in high-risk families (i.e., those with multiple cases of breast cancer across several generations) and who also carry a mutation in *BRCA1* have a 80-85% risk of developing breast cancer during their lifetime, while the risk of women with the mutation but without such a family history is 55-70% (14). In comparison to sporadic breast cancer, tumors associated with a mutation in the *BRCA1* gene are more poorly differentiated, of higher stage and grade, do not express hormone receptors and human epidermal growth factor receptor-2 (HER2) (Triple Negative Breast Cancer (TNBC)) and exhibit invasive ductal histology (15, 18, 19). Most, but not all women with such a mutation are diagnosed with breast cancer at a younger age.

Mutations in *BRCA2*, located on chromosome arm 13q, are known to be responsible for breast cancer in men, but are also linked to breast but not ovary cancer in women. Such tumors in women are well differentiated and express the estrogen receptor (ER)(15, 19). Although the risk of breast cancer is substantially higher among women who carry mutations in *BRCA1* or *BRCA2*, penetrance is not 100% i.e., not every carrier develops breast cancer (17).

Table 1: The frequency of BRCA mutations among different populations

General population prevalence	0.2%
Women with breast cancer at age 60	1%
Women with breast cancer at any age	5%
Women with breast cancer $\leqslant 35$	10%
Jewish women with breast cancer at any age	10%
At least 2 breast cancer < 50 in a family	12%
Women with ovarian cancer at any age	12%
Men with breast cancer	14%
Bilateral breast cancer	25%
Breast and ovarian cancer in one woman	33%
Jewish women with breast cancer at age 40 or younger	35%
Men with breast cancer and a relative with breast or ovarian cancer	36%
Jewish women with ovarian cancer at any age	48%

(Taken from Breast disease, 2006. **23**(1), James P. Evans, C´ecile Skrzynia, Lisa Susswein and Megan Harlanc, *Genetics and the young woman with breast cancer*, p. 17-29, Copyright (2005,2006), with permission from IOS Press)

2.2.1.2 Twins

Compared with singletons, twins are more commonly born preterm and with a low birth weight, due to the anatomy of the uterus and placental capacity (20). A discordance in the birth weights of twin siblings is common, especially at older gestational ages.

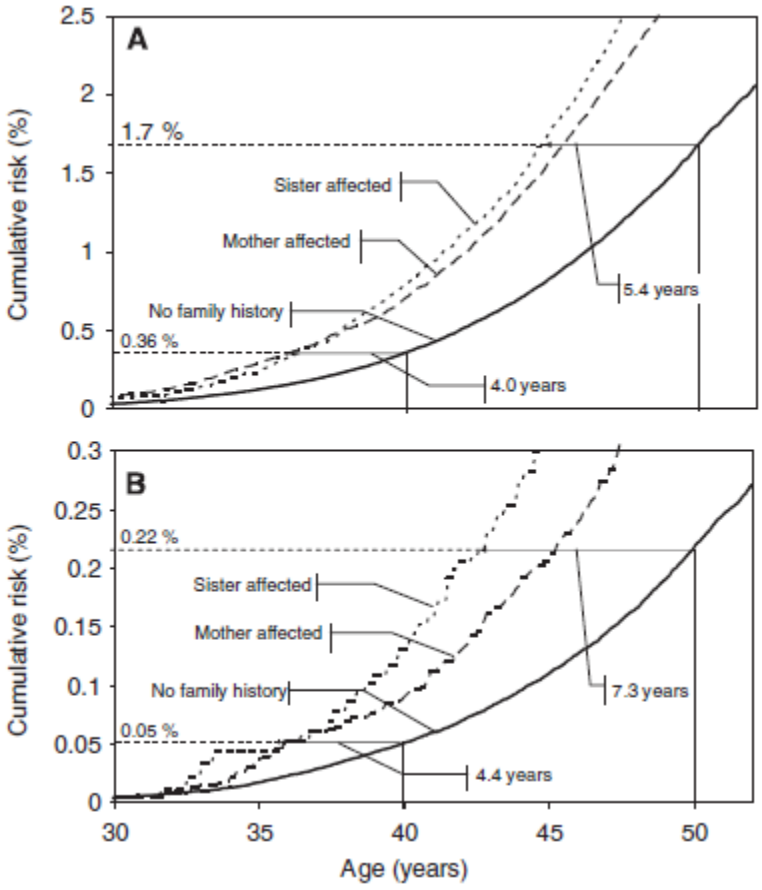
In addition, twin pregnancies are associated with higher and more varied levels of estrogens than singleton pregnancies (21-23). These levels are also higher in dizygotic (DZ) than in monozygotic (MZ) twin pregnancies (24). Since the placenta is the main source of hormones during pregnancy, the higher levels of estrogen in DZ twin pregnancies is probably due to the presence of two placentas. Since estrogen is a well-known risk factor for breast cancer, the higher levels of this hormone during pregnancy might elevate the risk of breast cancer (25).

The female member of twins of opposite-sexes may also exposed to androgens produced by their male co-twin (26). Glinianaia and colleagues (27) have shown that the birthweight of the female in twins of opposite sex is higher than when both twins are female. It is thought that androgens are responsible for the weight difference between male and female fetuses in connection with singelton pregnancies (26). Androgens compete with estrogens for binding to sex hormone binding globulin (SHBG) (26) and might thereby increase the level of bioavailable maternal estrogens, perhaps enhancing the risk of breast cancer.

2.2.1.3 Familial history

Having a first-degree relative (sister, mother or daughter) who develops breast cancer doubles a woman's risk of breast cancer (28, 29), and this risk is higher if the relative is the sister than the mother (Figure 5) (29-31). More specifically, the meta-analysis by Pharoah and colleagues (29) revelad that the relative risk of developing breast cancer was 1.9 if any first-degree relative had breast cancer, 1.8 in the case of daughters, 2.0 for mother and 2.3 for sisters, and highest among women with both a sister and mother with breast cancer (28). The elevated risk associated with a family history of breast cancer declines with increasing age (31-35). Based on a large population-based set of Swedish data, Brandt and colleagues (31) concluded that women with a family history of breast cancer were diagnosed and died from this disease at a younger age than those without a family history (Figure 5).

Figure 5: Cumulative incidence of breast cancer and cumulative risk of death by breast cancer according to the type of family history. (A) Age at which women with a family history reach the cumulative risk of women lacking a family history at the age of 40 and 50 years for incidence. (B) Age at which women with a family history reach the cumulative risk of women lacking a family history at the age of 40 and 50 years for death from breast cancer.



(Taken from Brandt, A., et al., *Age of onset in familial breast cancer as background data for medical surveillance*. British Journal of Cancer, 2009. **102**(1): 42-47, with permission from publisher)

2.2.2 Reproductive factors

Since measuring estrogen levels throughout a lifetime is difficult especially during the reproductive period, various indirect indicators have been developed, including age at menarche, age at first pregnancy, age at menopause, parity, gestational age and comorbidities related to pregnancy, such as pre-eclampsia, eclampsia, gestational hypertension and gestational diabetes. The relevance of such factors for the present work are discussed below.

2.2.2.1 Maternal characteristics

2.2.2.1.1 Age at first pregnancy

Later age at first pregnancy is a strong risk factor for breast cancer (12, 36, 37) and indeed, epidemiological studies have shown that each year of delay can increase the risk of breast cancer about 5% among premenopausal and around 3% among postmenopausal women (12). Being exposued to estrogen at a younger age could stimulate a higher proliferation of mammary cells which protect breast cells from being cancerous in future.

2.2.2.1.2 Age at last pregnancy

It has been reported that every 5-years increase in age at last pregnancy might elevate the risk of breast cancer by 5-8% (38, 39). However, Nechuta (40) did not find any association between these parameters.

2.2.2.1.3 Parity

Although one full-term pregnancy can reduce the overall risk of breast cancer during a woman's lifetime (41, 42), childbirth has a dual effect. There appears to be a short-term increase and a long-term decrease in risk after each pregnancy (43-45), effects that recur with each repeated pregnancy (45-47). With each full-term pregnancy, the risk of premenopausal breast cancer is reduced by 3%, while the reduction in postmenopausal breast cancer is 12% (12).

The effects of parity, age at first pregnancy, and age at last pregnancy on breast cancer risk may interact. For instance, women with higher parity often experience their first pregnancy at a younger age or the long-term protective effect of pregnancy in women who have two children is more dominant among those who were pregnant at a younger age (47). Therefore, when investigating the influence of parity on risk of breast cancer, it is important to control for the age at the time of pregnancy, the period that elapses between pregnancy and the diagnosis of breast cancer, and the intervals between pregnancies.

2.2.2.1.4 Maternal weight, height and body-mass index

Maternal body characteristics, including weight and height, have been associated with breast cancer risk in different studies. Some researchers tend combine these variables, e.g., in the Body-Mass Index (BMI, calculated as weight (in kilogram) divided by height (in meter^2), and

categorized as under weight (<18.5), normal weight (18.5 to <25), overweight (25 to <30) and obese (≥30). The association between BMI and breast cancer risk varies with other factors, such as age. For example several investigations have shown that obesity protects against breast cancer among premenopausal women (36, 48, 49), but enhances the risk among postmenopausal women (48-51). A meta-analysis of 13 studies revealed that for each unit increase in BMI breast cancer risk was reduced 2% in premenopausal and elevated 2% in postmenopausal women(52).

It has been proposed that premenopausal women with a high BMI have fewer ovary cycles which reduces their estrogen levels and in turn lowers their breast cancer risk (48, 53). In contrast, and despite cessation of ovary function in postmenopausal women, a higher BMI involves production of more estrogen by body fat tissue, which increases the risk. Indeed, postmenopausal women with a higher BMI exhibit higher levels of estrone, estradiol and free estradiol (50), as well as a lower level of SHBG, which enhance the bioavailablility of estrogen (48).

2.2.2.2 Characteristics of pregnancy

Pregnancy exerts a dual impact on breast cancer risk (43, 47), which increases during the first five years after pregnancy and declines thereafter (45, 47). Both the mother's age at the time of delivery and parity can influence this association. Albrektsen and colleagues (47) found that the short-term risk of uniparous women who deliver their first child before 25 years is the same as for nulliparous women, but those who give birth after 30 years exhibit on elevated risk of at least 15 years after delivery. Mothers who have two children and their second delivery happens at an age younger than 25 demonstrate a transient risk increase for breast cancer shortly after delivery and this adverse effect is more prolonged among older mother (>30 years of age). Apparently, age at third delivery is less important.

2.2.2.2.1 Gestational age of the child at birth

Estimation the precise gestational age (GA) i.e., the duration of pregnancy (55) from fertilization to delivery is virtually impossible. There are three indirect measures of the GA: the time that elapses between the first day of the last menstrual period (LMP) and delivery; ultrasound; and neonatal estimation (56). GA of <37, 37-42 and >42 completed weeks are commonly categorized as pre-term, term and post-term, respectively. Pre-term GA is subcategorized as <28 (extremely pre-term), 28-31 (very pre-term) and 32-36 weeks (moderate pre-term) (57).

Since estrogen levels increase as pregnancy progresses, the GA provides an indirect indication of this level. For example, Mucci and co-workers (58) reported that estrogens level are higher during the 27th than the 16th week of pregnancy and, moreover, that this increased level is associated with a higher later risk of breast cancer in the female offspring. Other investigators have found elevated breast cancer risk among offspring delivered before 32 (59, 60) or after 40 weeks of pregnancy (36). Russo and colleagues (61) proposed that since mammary cells proliferate during the first and second trimesters of pregnancy and differentiate during the third, shortening pregnancy holds mammary cells in proliferation phase, which makes them more prone to malignancy.

2.2.2.2.2 Placental weight

The placenta, a fetomaternal multifunctional organ of pregnancy, has an average length of 22 cm and thickness of 2–2.5 cm, being thickest in the middle. Its mean weight at a gestational age 40 weeks is 678 (±134) or 690 (±135) grams for a female or male fetus, respectively (62). The main functions performed by the placenta are nutrition, transporting oxygen and nutrients to the fetus, excretion, immunity and regulation of the endocrine status, becoming the primary steroid-producing organ during pregnancy (63).

During pregnancy, the placenta produces four dominant hormones, i.e., human chorionic gonadotropin (hCG), human placental lactogen (hPL), estrogen and progesterone. Previous work has revealed that placental weight can serve as an indirect indicator of estrogen levels during pregnancy (25, 63-67) and that breast cancer risk increases with placental weight (36). Thus, women whose placenta weighed more than 700 grams had a 38% higher risk of developing breast cancer than those whose placental weight was less than 500 grams (36).

2.2.2.3 Characteristics of the offspring

2.2.2.3.1 Birth weight, height and head circumference

It has been proposed that breast cancer may actually originate in utero (68). The level of estrogen, a well-known risk factor for breast cancer (see above), in the mother's blood is almost 200 times higher during than before pregnancy and it has been suggested that this exposure may be associated with the risk of breast cancer. Given the difficulty of directly and continuously measuring estrogen levels during pregnancy, some proxy measures have been considered. For instance epidemiological studies have reported that birth size (including weight, height and head circumference) are correlated with level of hormones, including estrogens during pregnancy (63, 69, 70).

Most investigations have found a positive association between birth weight and breast cancer risk in the female offspring (67, 71-79), particularly in premenopausal cancer (77, 80-86), whereas others observed no such association (66, 87-90). A literature review (91) of 26 relevant studies from 2000-2005 revealed that 16 found a positive association, three observed a positive, although not statistically significant association, and the remaining 7 found no association. In these studies the alteration in the risk of breast cancer with a birth weight of ≥4000 versus ≤2500 grams ranged from 17% to 5-fold. Moreover, it has been reported that breast cancer risk rises 9% for each 1000-grams increase in birth weight (92). Of the 14 studies dealing specifically with the association between birth weight and risk of breast cancer among the premenopausal female offspring (91), 11 showed a significant positive association between birth weight and risk of breast cancer, 5 of them showed a positive trend and 4 a threshold effect. Among the 8 studies on postmenopausal cancer (91), only one study observed an association.

Furthermore, offspring birth weight has also been associated with maternal risk of breast cancer. For example, Wohlfahrt and co-workers (25) have found that this risk is slightly higher (1.02, 95% CI 0.9-1.5) among mothers who deliver a heavy baby. In addition, Cnattingius and colleagues (36) found a positive association with risk of breast cancer among women who deliver two consecutive heavy babies (1.42, 95% CI 1.12-1.79), but that this elevation disappeared after adjusting for placental weight.

In addition to birth weight, an association between birth height and risk of offspring breast cancer has been reported (76), a stronger independent association than for birth weight or head circumference (76). It has been reported that this risk is 17% higher for women whose birth height was ≥51 cm and 11% higher for those whose head circumference was 31 cm (76).

2.2.2.3.2 The Ponderal index

Ponderal (PI) or Rohrer's index, an indicator of fetal nutritional status (63), is defined as the ratio between birth weight (in gram) divided by birth length (in centimeter^3)*100. Given the correlation between birth weight and height (76, 93), this could provide a suitable index of the combined effect of these two variables. This composite indicator of offspring nutritional status, which might be independent of race, gender and birth order (94), may be better than birth weight alone (95), as well as providing a useful indicator of fetal growth (94). PIs are categorized as low (PI<10%), appropriate (10%<PI≤90%) or high (PI>90%) (94).

PI is associated with maternal levels of estrogens during the reproductive period and pregnancy. Jasienska and colleagues (95) concluded from the association between PI and the level of estradiol (E2) that a higher PI may indicate a higher breast cancer risk. Moreover, Kaijser and co-workers (70) observed a positive association between PI and estriol levels (E3) during pregnancy.

2.2.2.3.3 Birth weight for gestational age (BW/GA)

BW/GA is defined as the ratio between the actual birth weight and that expected for the same gestational age and sex. Therefore, BW/GA might provide a better retroactive indicator of fetal growth than birth weight alone. This index can be categorized as very small for gestational age (VSGA) (<3%), small for gestational age (SGA) (3-<10%), appropriate for gestational age(AGA) (10-90%), i.e., normal (96, 97), large for gestational age (LGA) (91-97%) and very large for gestational age (VLGA) (>97%) (98). Nechuta and colleagues (40) observed that women whose offspring had a BW/GA of <10% demonstrated a lower risk of breast cancer among those who experienced their last pregnancy at the age of 30 or older (0.82, 95% CI 0.59-0.98).

2.2.2.4 Exposure to hormones

2.2.2.4.1 Estrogen

The steroid hormone group of estrogens induces responses in the reproductive tract, mammary tissue, and pituitary gland during the reproductive process, as well as playing roles in non-reproductive processes, such as bone formation and cardiovascular health (99). The ovary is the main source of estrogen during most of the reproductive period, except during pregnancy, when the placenta is the main source. In premenopausal women, the serum levels of estrogens, mainly in the form of estradiol (E2), is 100 pg/ml during the follicular phase and approximately 600 pg/ml at the time of ovulation, but levels of estrogen, mainly estriol (E3) elevats to nearly 20,000 pg/ml during pregnancy. The level of estrogen falls to less than 20 pg/ml after menopuase, when estrone (E1) becomes the dominant forms. The growth and differentiation of ductal cells in breast tissue are stimulated by estrogens, which also plays an indirect role in the development of the mammary glands (100).

Estrogen normally binds to SHBG (approximately 37%). “Non-SHBG-bound hormone” (approximately 2% free estrogen) and estrogen bound to albumin (approximately 61%) are referred to as bioavailable (101) and affect target cells, including both normal and malignant breast cells. The serum concentration of bioavailable estradiol is thought to be more strongly

associated with the risk of breast cancer than the total level of estradiol (101, 102). Estrogen bound to SHBG is also available to responsive tissues, where it reduces cell proliferation, so that a reduction in the binding capacity of SHBG results in more rapid proliferation in steroid-sensitive tissues such as breast cells (101). This binding capacity is lower in postmenopausal than premenopausal women (103) and an association between the levels of SHBG and ER has been detected in connection with postmenopausal, but not premenopausal breast cancer (103). From conception until the 30th week of pregnancy, the level of SHBG is 6 to 10-fold higher in pregnant women than in those who are not pregnant (104).

A number of investigations on the difference in serum estrogen levels between pregnant compared and non-pregnant women and its association with the risk of breast cancer have been published. One review (105) concluded that the mean estrogen level in premenopausal women is 12% higher in those diagnosed with breast cancer, while another similar review on postmenopausal women arrive at a 15% higher value for those with breast cancer (106). A meta-analysis on 9 prospective studies revealed that high levels of serum estrogen is associated with higher risk of postmenopausal breast cancer (107). It has also been reported that the elevated level of estrogen during the first trimester of pregnancy is positively associated with the risk of developing breast cancer before 40 years of age, but that this association becomes negative at more advanced age (108). Moreover, an European study observed that the estrogen levels in women diagnosed with breast cancer is higher than in control subjects three year prior to diagnosis (109). The association between estrogen and breast cancer risk appears to be independent of family history (110).

2.2.2.4.2 Progesterone

Progesterone is secreted by the ovary during most of the reproductive period, but primarily by the corpus luteum and placenta during pregnancy (63). The main responsibilities of progesterone are to prepare the uterine muscles for implementation of the fertilized ovum and then support the pregnancy by inducing the proliferation and differentiation of uterine muscles to protect early embryonic development. A possible association between the level of progesterone and risk of breast cancer remains unclear: certain reports have shown a negative association with premenopausal women (109, 111), while no association was found for postmenopausal women (112) or all cases of breast cancer (108, 112). However, estrogen and progesterone might interact to elevate the risk of breast cancer; the so-called (estrogen plus progesterone hypothesis) (109).

2.2.2.4.3 Androgens

Since androgens are the obligatory precursors of all endogenous estrogens and may play a role in cell growth and proliferation, they might also influence breast cancer risk, either directly and/or indirectly (113, 114). Their ability to stimulate the growth and proliferation of cells might affect this risk directly while conversion to estrogens represents indirect involvement. Postmenopausal breast cancer exhibits a positive association with higher levels of androgens (102, 107, 109, 112) and reanalysis of 9 prospective (107) and the other studies (109) reveals that this is an independent association. Tumors that express both ER and PR are correlated with higher concentrations of androgens, including testosterone, androstenedione and dehydroepiandrosterone sulfate, but not those that lack either or both of these receptors (112).

Among the few studies on the association between androgen level and risk of breast cancer in premenopausal women, two (115, 116) reported a positive correlation. Some studies report that this association is more pronounced in the case of invasive tumors (110, 117) and ER+/PR+ patients (110, 118), but the underlying mechanism(s) remains unclear.

2.2.2.4.4 Insulin-like growth factor 1(IGF1)

In the 1980's, it was postulated that IGF1, a peptide that stimulates mitosis and inhibits apoptosis in humans, is involved in the development of breast cancer (119). The serum concentration of IGF1 is higher in women with breast cancer than in those without breast cancer (120, 121). A review of 17 studies in 12 countries (119) concluded that the IGF1 level is positively associated to the risk of breast cancer and that this association is relatively unchanged by menopause. The level of IGF1 also positively associated with height, age at first pregnancy, moderately increased weight, and moderate alcohol consumption.

2.2.2.4.5 Prolactin

Prolactin, secreted by the pituitary gland, stimulates cell proliferation in the normal breast before and during pregnancy, as well as lactation following pregnancy. Certain investigators report that the serum level of prolactin is reduced after the first pregnancy (122). Moreover, this level is inversely correlated to age at first birth and the age when breastfeeding is begun (123). It has been proposed that prolactin is an important factor in the etiology of breast cancer, stimulating the proliferation of and inhibiting apoptosis in tumor cells (124, 125). Several studies have shown a positive association between the prolactin level and risk of

breast cancer among postmenopausal women (126-128), and one study (128) reported a similar association in premenopausal women.

2.3 Prognosis for women with breast cancer

Thanks to improved diagnosis, better staging of the tumor at the time of diagnosis and more effective treatment, mortality from breast cancer has been declining since the 1990s (129). Although many factors, such as those associated with reproduction are well-known risk factors for breast cancer (see above), their influence on breast cancer mortality is not as well known.

2.3.1 Genetic and environmental factors

2.3.1.1 *BRCA1*and *BRCA2*

Few investigations have focused on the impact of mutations in *BRCA1* and *BRCA2* on survival after developing breast cancer. Four of these studies observed no impact (130-133). In contrast, Robson and colleagues (134) reported that carrying a *BRCA1* mutation reduces survival, but only among women who have undergone breast-conserving treatment in connection with invasive breast cancer.

2.3.1.2 Family history

Some previous investigations have revealed that mortality from breast cancer is higher among women who have a positive family history (Figure 5) (31, 135, 136) , an effect that is age-dependent, being high pronounced at younger ages (136). Moreover, mortality, is higher among women whose sister, rather than mother was diagnosed with this malignancy (31). Certain other studies reported a higher survival of breast cancer in family history positive patients (137-140). Adjustment for potential confounders has confirmed that this favorable influence of a positive of family history is an independent effect (138). In a japenease study, women with a positive family history had smaller tumors, that expressed higher levels of ER+ and lower levels of HER2, as well as less lymph node involvement (141). However, the mechanism(s) underling the lower mortality from breast cancer among women with a positive family history is still not clear.

2.3.2 Reproductive factors

2.3.2.1 Maternal characteristics

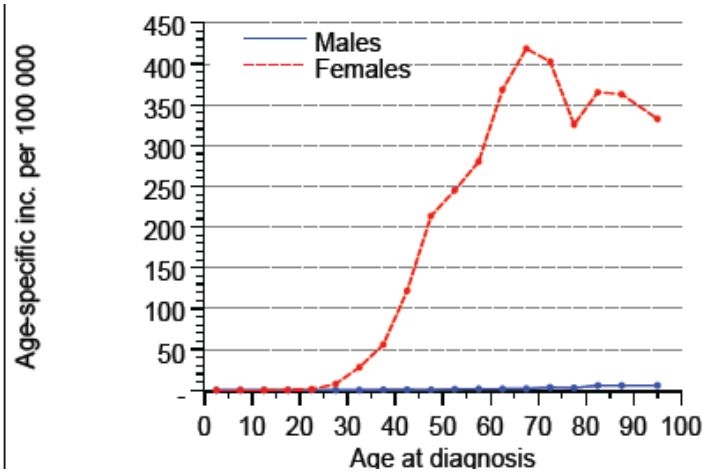
2.3.2.1.1 Age at the time of diagnosis

Age at diagnosis has been proposed to be a valuable prognostic factor for breast cancer survival. Breast cancer is relatively uncommon among young women, and only 15-25% of these patients are in their thirties or forties (142). Although the definition of "young" varies (49, 143), breast cancer in younger women is known to involve larger tumors, at a higher stage, lower expression of both ER and PR, higher levels of HER2, more extensive involvement of lymph nodes (144, 145), and poorer prognosis (146, 147).

It has been suggested that breast cancer should be categorized at the time of diagnosis as either premenopausal or postmenopausal. Some studies divide women with breast cancer into those whose are 50 or younger and those who are older, which corresponds roughly these same two categories (146, 148, 149). Although breast cancer is more frequent among 60-70-year old women (Figure 6), the disease is more often aggressive among women younger than 50 (Table 2). Moreover, mortality declines with increasing age at the time of diagnosis.

The inverse association between age at the time of diagnosis and the risk of dying from breast cancer has been addressed in several publications (150-152). Han and Kang (143) observed that breast cancer mortality risk increased by 5% for each year of reducing in age among women younger than 35, but not for those between 35 and 50 years of age. In fact, they found that the pattern risk of mortality from breast cancer differs for women younger than 35 and those who are older and therefore suggested that 35 years is a suitable cutoff for young cases of breast cancer. Despite these findings, age at the time of diagnosis is not considered to be an independent prognostic factor (142) and the higher mortality risk among younger patients might reflect the more serious nature of their tumors (142, 152).

Figure 6: Age distribution of women with breast cancer in Sweden in 2010



(Socialstyrelsen - The National Board of Health and Welfare, Official Statistics of Sweden, Statistics – Health and Medical Care, Cancer Incidence in Sweden 2010)

Table 2: Pathological features of breast cancer in premenopausal women

High grade
Poorly differentiated
High proliferative rate
Higher Ki-67 expression
Higher p53 expression
Lymphovascular invasion
Estrogen-receptor negative
Progesterone-receptor negative

(Reproduced from Vetto J. et al. *Current Problems in Surgery* 944–1004) with the permission of the publisher)

2.3.2.1.2 Age at first pregnancy

A younger age at first pregnancy in premenopausal women is associated with a higher breast cancer mortality rate (153-155). Although a study involving a population of more than 800,000 revealed that the mortality from premenopausal breast cancer was higher among women who had their first pregnancy after 30 years (153), other studies have reported that the risk of mortality from breast cancer is higher among women younger than 20 years at their first pregnancy than those between 20 and 24 (154, 155). Thus, although high age at first pregnancy is a risk factor for breast cancer, age at first pregnancy appears to be somewhat inversely associated with breast cancer mortality (155). It has been postulated that lower age at first pregnancy can prevent less aggressive forms of breast cancer. If so, the more aggressive forms that do develop might explain the higher risk of mortality associated with lower age at first pregnancy (154).

2.3.2.1.3 The time that elopes between pregnancy and the diagnosis of breast cancer:

Pregnancy-associated breast cancer (PABC) is defined as disease diagnosed during pregnancy or within 2 years after delivery (156). Several previous examinations have found that the risk of breast cancer is increased during the two years immediately after delivery, and some have shown that survival among women whose breast cancer is diagnosed during this period is reduced (156-165). For example Philip and co-workers (163) found that the risk of mortality from breast cancer was 1.7 for women diagnosed during the two years after pregnancy and 0.9 for those diagnosed five or more years after. Although there is one report that this risk is higher among women diagnosed within the first year after pregnancy (164), a Swedish study found maximal risk 4-6 months after pregnancy (156).

The reduction in breast cancer mortality risk associated with a longer time interval between last pregnancy and diagnosis persists for more than 10 years among women who were younger than 20 at their first pregnancy(154). No association between the time between the last pregnancy and diagnosis of breast cancer and survival was seen among postmenopausal women (157). Although certain studies claim that the overall survival of cases with PABC and other is the same (166), Philips and colleagues (163) concluded that this survival increases by 8% for each year that elapses after pregnancy; while another report (167) presented a corresponding values of 15%, although the sample size was small in this latter case.

Although it is unclear why the risk of mortality from breast cancer falls as more time elapses after delivery, one possible mechanism could involve changes during pregnancy, particularly in hormonal status (168) which might stimulate tumor growth and/or select for the growth of

more aggressive cancer cells (164). In addition, a longer delay before accurate diagnosis due to the increased density of the breasts of younger lactating women may play a role (163). It has also been proposed that the characteristics of the tumor are important in this connection.

Tumors diagnosed during first two years after pregnancy have been reported to be particularly aggressive (164, 165, 168) with a higher stage (160), an axillary node–positive nature (160, 163, 166), no expression of ER (159, 163, 166) or PR (159, 160, 166), a higher T class (159, 166), expression of p53 (160), a high mitotic count (160), with a fraction of cells in S phase (160), and a higher grade (160, 166). Thus, the association between diagnosis of PABC and risk of mortality from breast cancer has not been reported to be an independent prognostic factor (166) but, rather, to be confounded by the characteristics of the tumors (164). Certain other investigations suggest that additional, unknown characteristics of the tumors or pregnancy may exert an impact on this association (163).

2.3.2.1.4 Parity

Higher parity is associated with more extensive breast cancer mortality among premenopausal women (42, 157, 160, 161, 169, 170). For example, Olson and co-workers (42) found that the risk of such mortality is higher among women with three or more children than among nulliparous women. In contrast, certain reports indicate that parity either promotes (171) or has no effect on mortality from breast cancer, neither among premenopausal nor among postmenopausal women (155, 164). The tumors of parous women demonstrate a higher stage at the time of diagnosis, positive nodes and expression of p53 (160, 169).

2.3.2.2 The characteristics of pregnancy

2.3.2.2.1 Maternal weight, height and BMI

Some studies, including a literature review (48, 161, 172-174), show that most, but not all of the reports indicate that both overall and five-years survival from breast cancer is lower in pre- and postmenopausal women with higher BMI. Obesity is associated with cancer exhibiting less favorable features, including more nodule involvement (175) and a higher stage (176). In addition, a Norwegian study has shown that high body weight is associated with larger diameter, especially in the case of ER- and PR- negative tumors (177). Moreover, the risk of developing inflammatory breast cancer, the most lethal form, is higher among both pre- and postmenopausal women with higher BMI (48). In addition, all modalities of breast

cancer treatment, including surgery, radiotherapy, chemotherapy and hormone treatment, are reported to be adversely affected by obesity (48, 172).

2.3.2.2.2 Placental weight

The association between placental weight, suggested as an indicator of estrogen levels during pregnancy (58, 70, 178), and the risk of breast cancer has been examined by some investigators, but only one study has focused on the association between placental weight and breast cancer mortality risk. In this Swedish study, Larfors and colleagues (179) found that women whose placenta weighed 700 grams or more had an enhanced mortality risk, although they did not observe any significant association with other subgroups of placental weight. The association observed was more pronounced among uniparous women and those diagnosed with breast cancer during first two years after delivery.

2.3.2.3 Characteristics of the offspring

2.3.2.3.1 Birth size

Few investigations have examined the possible association between birth size and later offspring mortality from breast cancer. Sanderson and colleagues (180) reported that a birth weight of more than 4000 grams is associated with a higher subsequent breast cancer mortality risk. In addition, Norwegian researchers observed that a birth height of more than 52 cm was associated with a higher risk of mortality, but found no such associations with offspring birth weight or PI (181), which is in agreement with another study (155). Sovio et al. (182) have reported that the risk of mortality from breast cancer is increased 29% by an increase in birth weight by one standard deviation, with a weaker association for PI.

The possible association between offspring size and maternal breast cancer mortality risk has also been explored. Smith and co-workers (93) observed higher maternal mortality in association with higher PI, but no relationship to offspring birth weight or height. A meta-analysis revealed no association between birth weight and maternal mortality from breast cancer (183).

2.3.2.3.2 Gestational age

Little has been reported on the possible association between gestational age and mortality from breast cancer. Sanderson et al. (180) found no such association, whereas Sovio (182) reported 14-17% increased breast cancer mortality risk with an increase in gestational age by one standard deviation.

2.3.2.4 Tumor characteristics

2.3.2.4.1 Stage

Since 1953, solid tumors are categorized with staging system (184) (TNM, the latest edition of which was described in 2010 by the International Union Against Cancer (uicc) (185)), based on the size of the tumor (T), involvement of lymphatic system (N) and distribution throughout the body metastasis (M) as the primary prognostic factors. Based on this TNM, the American Joint Committee on Cancer (AJCC), has introduced a specific system for staging of breast cancer, (latest edition in 2009) (186), which is also used.

Various investigations have revealed that larger size, involvement of nodes and distant metastasis are poor prognostic factors for cancer. Higher tumor stage is associated with higher mortality (42, 187-189), but tumor size, nodule involvement and distant metastasis might valuable prognostic factors for individual breast cancers as well (42, 189). Previous findings indicate that axillary node involvement is the most independent indicator of overall survival from breast cancer (190), even if there is discordance between tumor staging and nodule involvement (191). Despite worldwide routine use of the TNM staging system for selecting the optimal therapeutic approach, there are suggestions that this system requires more refinement in order to become a really useful guideline for therapy (190, 192, 193).

It has been reported that the prognostic value of tumor size, nodule involvement and tumor grade decreases progressively with time (194, 195), although others suggest long-term effectiveness of these prognostic factors (196). One investigation including operable breast cancer cases found that the value of these prognostic factors tended to disappear after 10 years and that they were not related to mortality risk after 15 years (194).

2.3.2.4.2 Hormone receptors

The presence or absence of hormone receptors, including the ER and PR, individually or together has been suggested to be prognostic- and predictive factors for breast cancer. This expression increases with the age of the patient (197, 198) and the distribution of the receptors changes during the years following breast cancer diagnosis (199). Karlsson et al. (200) compared ductal carcinoma in situ with the subsequent nodule involvement found that 15% of the cases with ER expression and 30% of the cases with PR expression were changed in subsequent local relapse. Moreover, the prognostic value of hormone receptors appears to be short-time, and decreases with a long follow-up time (201-203). Bardou and colleagues (203) explained that, although women whose tumor is ER+/PR+, ER+/PR- or ER-/PR+ have

better survival than those with ER-/PR- tumors, this prognostic value disappears after 5 years, whereafter it becomes difficult to predict the future development of the tumor based on their receptor status. Notwithstanding, researchers still believe that breast cancer can be considered to be distinct diseases characterized by their hormone receptor status (204-208).

2.3.2.4.2.1 Estrogen receptors (ERs)

Estrogen receptors belong to a superfamily of nuclear receptors, including receptors for sex steroids, thyroid hormone and retinoid (99). The two different isoforms of ER, ERα and ERβ, are encoded on chromosomes 6 and 14, respectively (202, 209). A broad spectrum of tissues express ERα and ERβ; ERα is expressed at a higher level in the breast, prostate (stroma), ovary (theca cells), testis (Leydig cells), and liver, while ERβ is expressed more strongly in the prostate (epithelium), colon, testis, ovary (granulosa cells) and bone marrow (210).

In breast tissue, ERs are expressed by both normal and malignant cells. About 20% of the Terminal Duct Lobular Units (TDLU) in the breast of premenopausal women express the ER, a value that doubles during the follicular phase (211). The average extent of expression of ER by the TDLU cells of postmenopausal women is approximately 50%(211).

Expression of ERs increases dramatically in early hyper-proliferative premalignant lesions (211). Approximately 75% of breast tumors express ERs (211) with an elevated ratio of ER+ to ER- cells in comparison to normal breast tissue. Moreover, higher expression of ER is associated with higher breast cancer survival (212, 213). ER+ tumors tend to develop in older women (peaking of 70 years at age (214)), whereas ER- tumors tend to develop at an earlier age (peaking at 50) (49). Mortality from premenopausal ER+ breast cancer is higher in women younger than 35 than in older women (49).

2.3.2.4.2.2 Progesterone receptors (PRs)

Progesterone receptors belong to a nuclear or intracellular superfamily of ligand-dependent transcription factors (215, 216). After binding progesterone, PR changes conformation and is translocated to the nucleus, where it interacts with DNA to mediate the effects of progesterone (217, 218). In most target tissues, expression of PR is stimulated by estrogen (202) and reduced by progesterone.

The two isoforms of PR, PR-A and PR-B, are encoded by the same gene but their expression is initiated by different promoters (202, 215, 216, 219). Some studies suggest that expression

of PR is stimulated by atypia and increasing ratio of PR-A to PR-B, which is almost one in normal breast tissue, but varies extensively in malignant cells (220, 221). Approximately 60% of invasive breast tumors express PR-A or B (216).

2.3.2.4.3 Human epidermal growth factor receptor-2

Human epidermal growth factor receptor-2 (HER2) is a transmembrane tyrosine kinase receptor encoded on chromosome 17q21. HER2 is overexpressed in approximately 20-25% of invasive breast tumors as a result of gene amplification (222). This receptor has a role in regulating cell proliferation (50).

In newly diagnosed patients, HER2-positive breast cancer has a worse prognosis (50) and this factor may thus play a role in decision-making about treatment (223, 224). Such tumors are relatively resistant to endocrine therapy (222, 224, 225). Approximately 10% of primary HER2+ tumors becomes HER2- upon relapse (200). It has been reported that 6% of HER2- tumors becomes HER2+ during tumor progression and that 19% of HER2+ tumors becomes HER2-, although sample number in this case was small (226). The American Society of Clinical Oncology has suggested that HER2 expression should be used routinely as a prognostic- and predictive marker for breast cancer (222, 227)

2.3.2.4.4 Estrogen and progesterone receptors together

In light of the heterogeneity of breast cancer, it has been proposed that categorization should be based on expression of both ER and PR (207), which has a better and more independent prognostic value than their individual levels of expression (228, 229). ER+/PR+ tumors have a better prognosis than the other types of breast cancer (ER+/PR-, ER-/PR+ or ER-/PR-)(71, 228, 229), exhibiting smaller size, more favorable grade and better cancer-specific survival than ER-/PR- tumors (71). Among breast tumors, 60% are ER+/PR+, 15-20% ER-/PR-, 15-20% ER+/PR-, and less than 5% ER-/PR+ (71, 206-208).

Receptor status is associated with a number of factors, including maternal age, menopausal status, age at first pregnancy, nulliparity and age at menarche. ER+/PR+ tumors are much more common among older women, whereas ER-/PR- tumors are more frequent among younger patients (230). Thus, premenopausal women are diagnosed more after with ER-/PR- tumors, while ER+/PR+ tumors are more frequent after menopause (71). Some studies indicate that higher age at first pregnancy, nulliparity and later age at menarche exert stronger effects on the risk of developing ER+/PR+ than to ER-/PR- tumors in postmenopausal

women (207, 231). Others have shown that higher maternal BMI (232, 233) increases the risk of ER+/PR+ breast cancer. However, another investigation reported no influence of menstrual or reproductive characteristics and familial history on ER+/PR+ and ER-/PR- tumors (205).

2.3.2.5 Classification according to St Gallen procedure

In 2011, an expert panel of the 12th St Gallen International Breast Cancer Conference introduced a new procedure for classification of breast cancer into 5 different subcategories on the basis of hormone receptor expression and epithelial cellular origin for therapeutic purposes (Table 3) (4). Tumors are categorized as follows:Luminal A: ER+ and/or PR+, low Ki56 (<14%), HER2-. Luminal B: ER+ and/or PR+, high Ki56 (>14%), HER2-; or HER2+ with any expression of Ki56. HER2+ (Erb-B2 or non-Luminal): ER- and PR- but HER2+. Triple Negative Breast Cancer: ER-, PR- and HER2-.

Table 3: The luminal classification of breast cancer

Intrinsic Subtype (1)	Clinico-pathologic definition	Notes
Luminal A	**'Luminal A'** ER and/or PgR positive(76) HER2 negative (77) Ki-67 low (**<**14%)*	This cut-point for Ki-67 labelling index was established by comparison with PAM50 intrinsic subtyping (7). Local quality control of Ki-67 staining is important.
Luminal B**	**'Luminal B (HER2 negative)'** ER and/or PgR positive HER2 negative Ki-67 high	Genes indicative of higher proliferation are markers of poor prognosis in multiple genetic assays (78). If reliable Ki-67 measurement is not available, some alternative assessment of tumor proliferation such as grade may be used to distinguish between 'Luminal A' and 'Luminal B (HER2 negative)'.
	'Luminal B (HER2 positive)' ER and/or PgR positive Any Ki-67 HER2 over-expressed or amplified	Both endocrine and anti-HER2 therapy may be indicated.
Erb-B2 overexpression	**'HER2 positive (non luminal)'** HER2 over-expressed or amplified ER and PgR absent	
'Basal-like'	**'Triple negative (ductal)'** ER and PgR absent HER2 negative	Approximately 80% overlap between 'triple negative' and intrinsic 'basal-like' subtype but 'triple negative' also includes some special histological types such as (typical) medullary and adenoid cystic carcinoma with low risks of distant recurrence. Staining for basal keratins (79) although shown to aid selection of true basal-like tumors, is considered insufficiently reproducible for general use.

*This cut-point is derived from comparison with gene array data as a prognostic factor [7]. Optimal cut-points in Ki-67 labelling index for prediction of efficacy of endocrine or cytotoxic therapy may vary.
**Some cases over-express both luminal and HER2 genes.

(Reprinted from Goldhirsch, A., et al., Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Annals of Oncology, 2011. 22:1736-1747. With permission from the publisher)

Luminal A tumor has a more favorable prognosis than the Luminal B subtype. TNBC tumors, which constitute 10-20% of breast cancer tumors, have a higher mortality rate and higher probability of distant metastasis than other subtypes of breast cancer (4, 51, 234). There is some discordance between the expression of factors in the original breast tumor and in lymph node metastases, as well as in the original tumor and relapse. For example, Falck and colleagues (234) showed 11% discordance between original tumors and with lymph node metastases and 16% of original Luminal A tumors were of a better subtype than lymph node metastases. Wilking and colleagues (226) found that in 15% of patients with HER2+ or HER2- original breast cancer, the recurrent tumor was of the opposite type. Moreover, Lindström and co-workers (235) found that 32.4% of ER+, 40.7% of PR+ and 14.5% of HER2+ original tumors change to the negative status upon relapse.

2.4 Mechanism(s) underlying the development of breast cancer

2.4.1 Normal maturation of the breast

Mammary glands in women start to develop at the puberty, when the ductal structure begins to enlarge and branch by the beginning of the menstrual cycle. At onset of puberty, the epithelial cells in the ducts start to proliferate and form a tree-like pattern from the nipple to the end of the buds. Terminal Ductal Lobular Units (TDLU) develops and become more complex during subsequent menstrual cycles. The tree-like structures in the mammary gland are lined by epithelial cells and are surrounded by myoepithelial cells, which are in touch with basement cells. The TDLUs are embedded in fat tissue and surrounded by stromal cells (Figure 7) (216, 236, 237).

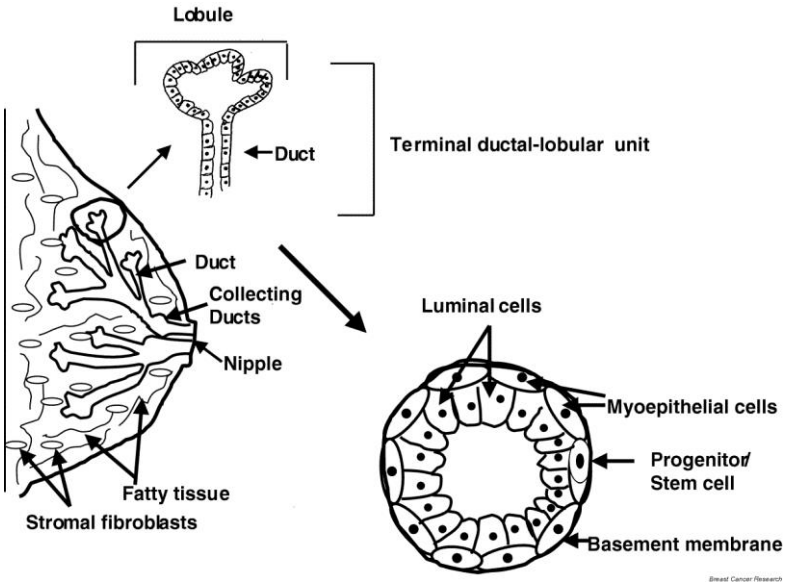


Figure 7: Structure of the mammary gland and terminal ductal–lobular unit (TDLU).
(Taken from Dimri et al. Breast Cancer Research 2005 7:171-179. With permission from the publisher)

Development of the breast normally starts 3 years prior to menarche. Many hormones, and especially the female sex steroids estrogen and progesterone, are required for the proliferation and development of mammary cells. The minimal hormonal requirement in this connection includes estrogen, progesterone and prolactin or growth hormone (237). Estrogen produced by the ovary is primarily responsible for the development of breast stroma, growth of the ducts, and deposition of fat; while progesterone promotes lobular growth, alveolar budding and alveolar secretory changes. Both estrogen and progesterone are necessary for complete maturation of the ductal alveolar system (238).

At onset of pregnancy, the epithelial cells of the breast begin to divide again, a process which continues until delivery. The ductal trees expand and the number of ductules in the TDLUs increases during early pregnancy, and the ductules become mature to produce and secret milk during the last period of pregnancy and lactation. When lactation starts, epithelial DNA synthesis begins, but ends after lactation is completed, when the glands are switched off until onset of the next pregnancy. Thus, during pregnancy and during lactation, the breast tissue evolves from immature to fully developed (204, 237, 239).

2.4.2 Tumorogenesis

Histology reveals that the TDLU are the main origin of breast cancer in women. Moreover, since estrogen and progesterone receptors are expressed only in the luminal epithelial cells of these ducts, these cells could be in initial site of malignant transformation (204). Malignant cells may stay where they are, giving rise to Ductal Carcinoma In Situ (DCIS), the most common histological variant of the non-invasive stage of breast cancer. They may also penetrate the basal cells and extend to other parts of the body, resulting in, for example Invasive Ductal Cell (IDC), which accounts for 85-90% of all cases of invasive breast cancer (236).

The endogenous levels of steroid hormones fall sharply after menopause, due to the cessation of ovarian activity. At this point, adipose tissue becomes the main source of estrogen (102, 236). High levels of estrone (E1), the dominant form of the circulating hormone during postmenopausal period (102) is associated with a higher risk of postmenopausal breast cancer. Higher levels of estradiol and testosterone are also known to be associated with an enhanced risk of breast cancer (126, 240).

3. Aim of the present study

Main aim

To examine the independent association of indirect markers of pregnancy hormone exposure with breast cancer risk and survival, with special emphasis on young patients.

Aims of the individual studies

- To investigate whether tumor characteristics modify the association between placental weight and maternal mortality from breast cancer.

- To examine possible associations between offspring size at birth from the most recent pregnancy before diagnosis of premenopausal breast cancer and maternal risk of breast cancer mortality, taking tumor characteristics into consideration.

- To explore the association between birth weight and offspring risk of breast cancer in females in opposite sexed twin pairs.

  To investigate whether prenatal exposure to androgens from a twin brother influences the risk of breast cancer in the female twins, using male co-twin's birth weight as an indicator of androgen exposure.

- To examine whether associations between reproductive factors and risk of breast cancer are modified by genetic or early environmental factors.

4. Methodological considerations

4.1 Registries

4.1.1 The Medical Birth Register (MFR) (Studies I, II, IV)

The Medical Birth Register (MFR), maintained by the Swedish National Board of Health and Welfare, includes prospectively collected information during pregnancy, delivery, and the neonatal period on virtually all births in Sweden since 1973 (241, 242). From 1973-1981, data were collected with a medical record form used by all antenatal care clinics, a form used by delivery units and a form for pediatric examination of offspring. The data from these three forms were summarized by a secretary in a single new form and sent to the National Board of Health for computerized storage. From 1982 onwards, copies of the three forms listed above were sent directly to the National Board of Health and Welfare (241). A report by MFR in 2003 (242) showed that approximately 1.4% of all infants born in Sweden were not covered by this registry. Moreover, information on birth weight was a lacking in about 0.32% of cases. Information on placental weight, available only from 1982 to 1989, was missing for 21% of single births during this period.

4.1.2 The Swedish Quality Registry of Breast Cancer (SQRBC) (Studies I, II)

The Regional Quality Registries on Breast Cancer contain information collected since 1992 in the six geographically defined health care regions of Sweden. This information includes tumor characteristics, such as stage at diagnosis (tumor size, lymph node involvement, and existence of distant metastases) and biological characteristics (grade and hormone (estrogen or progesterone) receptor status), diagnostic procedures and treatment. The Regional Quality Registries are validated with regards to the capture of incident breast cancer cases by comparison with the national Swedish Cancer Register (SCR), and are more than 95% complete (243). For tumor characteristics, completeness is highest in the quality registries covering the Stockholm-Gotland and Uppsala-Örebro regions in central Sweden.

4.1.3 The Swedish Twin Registry (STR) (Study III)

The Swedish Twin Registry (STR), maintained by the Department of Medical Epidemiology and Biostatistics, at Karolinska Institutet, was established in the late 1950's. This registry, initially designed to investigate associations between cigarette smoking and alcohol consumption and cardiovascular disease and cancer, covers all twins born in Sweden since 1886, in the form of an older (1886-1925), middle (1926-1958) and younger cohort (1959-

present). Moreover, several questionnaires (administered in 1961, 1963, 1967, 1970 and 1973), a telephone interview (SALT) conducted between 1998 and 2002 (244), the Study of Twin Adults: Genes and Environment (STAGE) on twins born from 1959-1985, another study on twin children born since 1992 (the Child and Adolescent Twin Study in Sweden, CATSS) and a third study in which birth information on all twins born from 1926 to 1958 was collected were all used to complete the registry (245). Zygosity is based on the extent of similarities between twins (intrapair similarities) during childhood, a procedure shown by DNA analysis to be 98% accurate or more (244).

4.1.4 The Swedish Cancer Register (SCR) (studies III, IV)

The Swedish Cancer Register (SCR) has collected data on all cases of primary cancers in Sweden since 1958. Reporting of newly detected cancer is obligatory for all health care providers in Sweden by law. Information on the pathology and cytology of cancers obtained from surgically removed tissue, bone marrow aspiration, biopsies, and autopsies are reported separately to this registry. In addition to patient characteristics, including sex, age, place of residence and personal identification number, the medical information on the tumor includes the site, histology, stage and date of diagnosis. Moreover, follow-up data including date of death, cause of death or date of migration are added to this registry from the Swedish Cause of Death and Migration Registries(2). Approximately 98% of cases are verified morphologically(2). The SCR (243) is more than 98% complete (246) and is updated annually. Different editions of the International Classification of Diseases (ICD) have been used in the registry, but all have been translated to ICD-7 to enable studies of longer trends. A WHO method of coding pathology is used to record histological type, where applicable.

4.1.5 The Swedish Cause of Death Register (SCDR) (studies I, II, III, IV)

The nationwide Cause of Death Registey (SCDR) contains information on all deaths among Swedish residents since 1960. This information is based on death certificates filled in by trained physicians and contains the date of death, main and contributory causes of death, coded according to the ICD, 7^{th}–10^{th} versions. This registry has been maintained by National Swedish Board of Health and Welfare since 1994 (247).

4.1.6 The Multi-Generation Register (MGR) (Study IV)

The Multi-Generation Register, maintained by Statistics Sweden, collects information on all Swedish residents born after 1931 and still alive in 1961 as well as all those born thereafter. Thus, individuals born from 1932 and onwards are included in this registry (index persons).

The MGR contains information on the biological parents, siblings, children and cousins of index persons (2, 248). The completeness of the registry increased from 1961 to 2001, when it was considered complete since 2001 (249), covering information on 97% of mothers and 95% of all index persons (248).

4.2 The individual Studies

All four studies were pre-approved by the Regional Research Ethics Committee at Karolinska Institutet.

4.2.1 Study I

4.2.1.1 Data collection

Of all the women diagnosed with breast cancer during 1992 and 2006 (N=40,948), 8508 were diagnosed before menopause. All breast cancer information was extracted from the Regional Quality Registries of breast cancer for the Stockholm-Gotland and Uppsala-Örebro regions. After merging this information with data from MFR, excluding nulliparous women and women for whom information on placental weight was lacking, and restricting the study to the period 1982-1989, 1109 premenopausal parous women diagnosed with breast cancer remained. We subsequently excluded 8 women for whom information on gestational age was lacking, and 34 women with implausible information on placental weight. Of those excluded, 24 were recorded as premenopausal on the basis of self-reporting at the time of diagnosis, but were 55 years old or older according to registries. In total, 1,067 women were finally eligible to be included and were followed until emigration, death or end of follow-up (December 31st, 2008), whichever occurred first.

4.2.1.2 Statistical analysis

Cox regression analysis was used to estimate the hazard ratio (HR) between placental weight and risk of breast cancer mortality (with 95% confidence interval, CI) among premenopausal women. The follow-up period was the underlying time scale. By including time-by covariate interaction in the model and testing for statistical significance, the assumption of proportionality was verified for all of these analyses.

Placental weight was used as a continuous, as well as a categorical variable. To ensure that a sufficient number of subjects and events had been included in each category, placental weight

was divided into <600, 600-699 and ≥700 grams. First, the risk of mortality from breast cancer was estimated for the different categories of placental weight. Then, stratified analyses were performed to estimate this risk among different sub-categories of tumor characteristics. After these crude estimations, adjustments for gestational age (≤36, 37–38, 39–41, and ≥42 weeks), parity (1, 2, 3, and ≥4), age at diagnosis (<30, 30–34, 35–39, 40–44, 45–49, and 50–54 years), and level of education (less than high school, high school, and more than high school) were performed for all analyzes.

To investigate interaction effects, placental weight (a categorical variable), tumor stage, ER and PR status, and tumor histology (categorical variables) were incorporated into the full models. To estimate the risk of mortality associated with placental weight while taking tumor characteristics into consideration, stratified analyses of subjects with tumors of different stages (0–1, 2, or 3–4), ER status (ER+, ER-), PR status (PR+, PR-), joint receptor status (ER+PR+, ER+PR-, ER-PR+, ER-PR-) and histology (Ductal, Lobular, Other) were performed.

4.2.2 Study II

4.2.2.1 Data collection

Using the SQRBC covering the Stockholm-Gotland region and Central Sweden, women who received a diagnosis of premenopausal breast cancer between 1992 and 2008 were identified. These registries include self-reported information concerning menopause. Through a linkage to MFR, all parous women diagnosed with premenopausal breast cancer before pregnancy (n=6,129) were included. Women with missing data on birth weight or gestational age (n=41), whose pregnancies ended with stillbirth (n=18), and twin pregnancies (n=51) were excluded, giving a final total of 6019 subjects with premenopausal breast cancer. The outcome was death due to all causes, recorded for approximately 99% of all deaths. We followed the subjects from the date of diagnosis until emigration, death or end of follow-up (December 31st, 2009), whichever occurred first. Information about vital status and dates of emigration was retrieved from the Swedish Population Register and the highest level of educational from the Education Register.

4.2.2.2 Statistical analysis

The hazard ratio (HR) with 95% confidence interval (CI) was used as a measure of the association between BW/GA and risk of mortality from premenopausal breast cancer and was estimated using the Cox proportional hazards model. BW/GA was estimated using the Swedish reference curve for intrauterine growth and defined as the ratio of the observed to the expected. BW/GA was divided into <3, 3-9, 10-90, 91-97 and >97 percentiles.

The association between PI and birth weight adjusted for gestational age was estimated, using the exposure as a continuous and categorized variable. PI was divided into percentile ranges analogous to the categorization of BW/GA. The association between birth weight and risk of mortality from breast cancer was estimated with the birth weight as a continuous or categorical variable (<3000, 3000-3499, 3500-3999 and ≥4000 grams). All models were adjusted for age at the time of diagnosis (<30, 30-34, 35-39, 40-44, 45-49, and 50-54 years), gestational age (≤36, 37–38, 39–41, and ≥42 weeks), parity (1, 2, 3, and ≥4), and level of education (less than high school, high school, and above high school).

Maternal risks of mortality from breast cancer in relation to tumor stage (0-1, 2, or 3-4), estrogen receptor status (ER+, ER-), progesterone receptor status (PR+, PR-), joint receptor status (ER+PR+, ER-PR+, ER+PR-, ER-PR-) and histology (Ductal, Lobular, Other) were estimated by stratified analyses. To ensure a sufficient number in each sub-category, three stage categories were used instead of the five suggested by the American Joint Committee on Cancer (AJCC). The follow-up period was the underlying time scale. The assumption of proportionality was verified for all models by including time-by covariate interaction and testing for statistical significance.

4.2.3 Study III

4.2.3.1 Data collection

Data on 13,075 opposite-sexed twin pairs with birth characteristics, born during the period 1926-1972 were retrieved from the STR. Through linkage to the SCR, all twins with a diagnosis of breast cancer between 1972 and 2008 were identified and a nested case-control study was performed. Cases with breast cancer were individually matched to five female twins who were not affected by breast cancer by date of birth. Controls were alive when their counterpart case received the diagnosis of breast cancer. In total, 543 breast cancer cases and 2,715 controls were included.

The birth weight of the cases, controls and co-twins was divided into <2000, 2000-2499, 2500-2999, 3000-3499, and ≥3500 grams. The quartiles for birth height (≤46, 47-48, 49, and ≥50 cm) and head circumference (<32, 32-33, 34-35, and >35 cm) were based on the distributions of these values among the control subjects. GA was categorized (<33, 33-36, 37-39, and ≥39 completed weeks), and maternal age stratified as <25, 25-29, 30-34, and ≥35 years. Maternal parity at the time of the subject's birth was categorized as uniparous or multiparous. The maternal hypertensive diseases recorded during pregnancy included preeclampsia and eclampsia. Socioeconomic status was based on the father's profession at the time of birth (unskilled blue-collar worker, skilled blue-collar worker, low-level white-collar worker, intermediate-level white-collar worker, high-level white-collar worker or self-employed). If information on the father's profession was missing, the mother's profession was used.

4.2.3.2 Statistical analyses

The association between birth weight and risk of breast cancer was estimated by conditional logistic regression. First, crude odds ratios (OR) and 95% confidence interval (CI) were estimated. Birth weight was considered both as a continuous (increase in risk per kg increase) and a categorical variable (<2000, 2000-2499, 2500-2999, 3000-3499, and ≥3500 grams) to estimate breast cancer risk. To decrease limitations due to the relatively small number of subjects in each category, we also reanalyzed the data using three categories of birth weight (<2500, 2500-2999 and ≥3000 grams).

After executing this crude model, we consecutively adjusted for potential confounding factors in three different models, i.e., gestational age; then maternal age, parity and hypertensive disease during pregnancy; and finally socioeconomic status. The numbers of cases/controls for whom information concerning maternal parity and socioeconomic status was missing were 45/225 and 167/897, respectively. The association between co-twin birth weight, utilized as an indicator of the influence of androgen exposure, and breast cancer risk was also estimated, as was the association between the difference in the birth weights of the twin brother and sister (as a continuous or categorical variable (500 gram categories)) and breast cancer risk. Since the etiologies of pre- and postmenopausal breast cancer differ, theses analyses were stratified by age at the time of diagnosis, using 50 years as the boundary between pre- and postmenopausal breast cancer. We used multiple imputation procedures to

deal with the missing values (250) and the Box–Tidwell test to examine possible nonlinearity of continuous variables.

4.2.4 Study IV

4.2.4.1 Data collection

In order to conduct a case-control study on possible modifying impact of familial factors on the association between early life events and risk of breast cancer, all women with singleton births in Sweden between 1973-2010 who had at least one full sister were identified from the MFR linked to MGR. By linking to the SCR, all women subsequently diagnosed with breast cancer at or before 50 years and who had a sister giving birth during the same period were selected for analysis.

Both sisters and the general population were used as controls. Sister controls were parous sisters not diagnosed with breast cancer, closest in age to their sisters with breast cancer and alive at time breast cancer was diagnosed. All parous women in the study population who were not diagnosed with breast cancer and not a sister of a patient served as the population controls. In total, there were 8,349 cases, 8,349 sister controls, and 1,053,688 population controls.

4.2.4.2 Statistical analyses

To estimate the OR with 95% CI of breast cancer risk in association with birth and maternal characteristics, we used conditional logistic regression models or logistic regression models. The birth weight from the latest pregnancy was considered as a continuous and a categorical variable (<2500, 2500-2999, 3000-3499, 3500-3999, 4000-4499 and ≥4500 grams). We also estimated associations between BW/GA as a continuous and a categorized variable (<3, 3-<10, 10-90, 91-97 and >97 percentiles) and breast cancer risk. Since infants within the 10-90 percentiles are considered "Appropriate for Gestational Age (AGA)", they were used as the reference group.

Adjustments for maternal age at latest pregnancy (<25, 25-29, 30-34, 35-39, ≥40 years), parity (1, 2, 3, and ≥4), level of education (below high school, high school, and more than high school) and date of birth (1973-1979, 1980-1989, 1990-1999, 2000-2010) were performed. Birth characteristics were also adjusted for these parameters plus GA (≤31, 32-36, 37-38, 39-41 and ≥42 weeks). In addition to achieve a sensitivity analysis, the model for birth characteristics was adjusted for all variables used in the previous model, except GA.

Moreover, to control for potential confounders, we also adjusted for maternal height (<163, 163-166, 167-170, ≥171 cm) and maternal BMI (<19, 19-24, 25-29 and ≥30) from 1983. No information on maternal BMI and maternal height was available for 1990 and 1991, and the percentage coverage for the other years ranged between 73 and 88%. We also analyzed the data from the perspective of first pregnancies during the study period (n=6,945) to study any association between age at first pregnancy and premenopausal risk of breast cancer.

All analyses were performed using the SAS software (SAS Institute, Cary, NC, USA).

5. Results

5.1 Study I

The major finding was that the association between placental weight and higher risk of mortality from breast cancer is more pronounced for women with ER-/PR- tumors. The crude RR for higher maternal mortality was statistically significant for women with a placental weight between 600 and 699 grams in their last pregnancy before diagnosis (Table 4), but a heavier placenta did not increase breast cancer mortality risk. A stratified crude and adjusted analysis revealed a significant association between placental weight and mortality from breast cancer for women with tumors in stage 3 or 4. Moreover, women with ER- or PR-negative tumors and a placental weight between 600-699 grams exhibited a higher risk of mortality from breast cancer. Subsequent analysis revealed that this association is more pronounced among women with ER-/PR- tumors (Table 5).

Table 4: Crude hazard ratios (HR) and 95% confidence interval (CI) for the association between placental weight and breast cancer mortality. Parous women with premenopausal breast cancer diagnosed from1992 through 2006

	Subjects	Events	Crude HR (95% CI)
Total	1067	180	
Placental weight, grams			
<600	458	70	Referent
600-699	322	69	1.49 (1.07-2.08)
≥700	287	41	0.90 (0.61-1.32)
Continuous (50 gram)	1067	180	1.00 (0.94-1.05)

Table 5: Crude and adjusted hazard ratios (HR) and 95% confidence interval (CI) for the association between placental weight and breast cancer mortality among premenopausal women with estrogen- and progesterone- negative tumors whose last pregnancy occurred during the period 1982-1989.

	Subjects	Events	Crude HR (95% CI)	Adjusted HR(95% CI)*
Placental weight, gram				
<600	56	9	Referent	Referent
600-699	48	16	2.29 (1.01-5.18)	2.69 (1.12-6.47)
≥700	44	18	3.06 (1.37-6.82)	3.86 (1.56-9.57)
Continuous (50 gram)	148	43	1.15 (1.02-1.30)	1.17 (1.03-1.32)

* Adjusted for gestational age, parity, age at diagnosis, and level of education

We found that the maternal risk of breast cancer mortality was reduced with more advanced age at the time of diagnosis and higher level of education. Moreover, women diagnosed with breast cancer less than 10 years after their last pregnancy had a higher risk of dying than those diagnosed later. As expected, a higher tumor stage, lack of both estrogen and progesterone receptors, were also associated with higher breast cancer mortality. We found no influence of GA, parity and age at first pregnancy on this risk in premenopausal women. In interaction analysis, we found significant association between placental weight and ER status and risk of breast cancer mortality ($p<0.01$), and a similar interaction was also found for PR status ($p<0.0001$).

5.2 Study II

We found no statistically significant association between offspring birth weight and maternal risk of mortality from breast cancer, neither in the crude analysis, nor in the adjusted analysis. Application of BW/GA showed a higher risk of women whose children had the lowest values (<3%) in the adjusted analysis (Table 6). There was no association between PI and maternal risk of mortality from breast cancer. The elevated risk among the women with the smallest offspring was restricted to those with cancer diagnosed 5–9 years after the pregnancy, 40 years or younger at the time of diagnosis and with stage 2 and/or ER-positive tumors.

Table 6: Crude and adjusted hazard ratios (HR) and 95% confidence intervals (CI) for the association between offspring birth weight and birth weight for gestational age and the maternal risk of breast cancer mortality. Premenopausal parous women diagnosed with breast cancer from 1992-2009 in Sweden.

	Subjects	Events	Crude HR (95% CI)	Adjusted HR (95% CI)a
Birth weight (grams)				
<3000	783	132	1.07 (0.88-1.31)	1.12 (0.90-1.40)
3000-3499	1862	330	1.12 (0.96-1.30)	1.13 (0.97-1.32)
3500-3999	2162	337	Referent	Referent
4000-4499	971	181	1.18 (0.99-1.41)	1.16 (0.97-1.40)
≥4500	241	37	1.04 (0.74-1.45)	1.06 (0.75-1.49)
P for trend			0.42	0.42
Continuous (100 grams)	6019	1017	1.00 (0.99-1.01)	1.00 (0.99-1.01)
Birth weight for gestational age percentiles				
<3	132	33	1.52 (1.07–2.15)	1.55 (1.09–2.21)
3-<10	294	60	1.15 (0.89-1.50)	1.09 (0.84-1.42)
10-90	4865	801	Referent	Referent
91-97	493	88	1.08 (0.87-1.35)	1.12 (0.90-1.39)
>97	231	35	1.00 (0.71-1.40)	1.05 (0.75-1.48)
Continuous	6015	1017	0.97 (0.91-1.02)	0.99 (0.93-1.04)
Information missing	4	0		
Quadratic analysis			1.03 (1.00-1.06)	1.04 (1.01-1.07)

[a]Adjusted for gestational age, parity and level of education

Estimation of the crude and adjusted hazard ratios for pregnancy characteristics and maternal risk of premenopausal breast cancer mortality revealed that lower age at the time of diagnosis, a lower level of education and a shorter period between the last pregnancy and diagnosis of breast cancer were associated with higher risks. Moreover, higher tumor stage, lack of ER and PR, in particular an ER-/PR- phenotype were associated with higher maternal mortality of breast cancer. Restricting the analysis to women born in Nordic countries (i.e., Sweden, Denmark, Finland, Iceland, and Norway) did not influence the results.

5.3 Study III

In the study of females from opposite-sexed twin pairs, we found no significant associations between birth weight and subsequent risk of breast cancer, neither for premenopausal (Table 7) nor postmenopausal women (Table 8).

Table 7: Crude and adjusted odds ratios (OR) and 95% confidence interval (CI) for the association between birth weight and risk of breast cancer in females of opposite-sexed pairs. Swedish twins born from1926-1985 and diagnosis at or before 50 years of age*

	No. (case/control)	OR (95% CI) Crude	OR (95% CI) Model 1	OR (95% CI) Model 2	OR (95% CI) Model 3
Birth weight, gr					
<2000	17/77	1.11 (0.62-1.98)	1.11 (0.59-2.09)	1.09 (0.58-2.06)	1.08 (0.57-2.04)
2000-2499	59/262	1.06 (0.72-1.55)	1.10 (0.74-1.63)	1.09 (0.73-1.62)	1.07 (0.72-1.60)
2500-2999	74/372	Referent	Referent	Referent	Referent
3000-3499	40/222	0.81 (0.53-1.25)	0.84 (0.54-1.30)	0.84 (0.54-1.30)	0.83 (0.53-1.30)
≥3500	13/42	1.56 (0.80-3.05)	1.70 (0.85-3.40)	1.72 (0.86-3.44)	1.75 (0.87-3.53)
Overall, Kg	203/975	0.95 (0.70-1.31)	0.99 (0.69-1.42)	1.02 (0.71-1.47)	1.01 (0.70-1.46)

*Multiple imputation analysis was used to deal with missing data.
Model 1: Adjusted for gestational age
Model 2: Adjusted for gestational age, maternal age, parity and hypertensive disease during pregnancy.
Model 3: Adjusted for the variables in Model 2 and social economy status.

Table 8: Crude and adjusted odds ratios (OR) and 95% confidence interval (CI) for the association between birth weight and risk of breast cancer in females of opposite-sexed pairs. Swedish twins born from 1926-1985 and diagnosed after 50 years of age *

	No. (case/control)	OR (95% CI) Crude	OR (95% CI) Model 1	OR (95% CI) Model 2	OR (95% CI) Model 3
Birth weight, gr					
<2000	26/133	0.88 (0.56-1.40)	0.85 (0.52-1.40)	0.84 (0.51-1.38)	0. 84 (0.51-1.38)
2000-2499	97/508	0.88 (0.66-1.17)	0.85 (0.63-1.14)	0.85 (0.63-1.15)	0. 86 (0.64-1.16)
2500-2999	138/645	Referent	Referent	Referent	Referent
3000-3499	64/382	0.78 (0.56-1.08)	0.79 (0.57-1.09)	0.78 (0.56-1.09)	0.77 (0.55-1.08)
≥3500	15/72	0.97 (0.54-1.75)	0.98 (0.54-1.78)	0.98 (0.54-1.79)	0.99 (0.54-1.80)
Overall, Kg	340/1740	0.97 (0.77-1.24)	1.03 (0.79-1.35)	1.03 (0.78-1.36)	1.03 (0.78-1.36)

*Multiple imputation analysis was used to deal with missing data.
Model 1: Adjusted for gestational age
Model 2: Adjusted for gestational age, maternal age, parity and hypertensive disease during pregnancy.
Model 3: Adjusted for the variables in Model 2 plus socioeconomic status.

Furthermore, there were no associations between birth height, head circumference, GA, maternal age, maternal parity and hypertensive disease during pregnancy and risks of premenopausal or postmenopausal breast cancer. We found no association between co-twin's birth weight and risks of pre- or postmenopausal breast cancer risk. In addition, there were no significant associations between the difference in female and male birth weight (as a continuous or categorical variable) and risk of premenopausal or postmenopausal breast cancer, even after application of the multiple imputation procedure to deal with missing data.

5.4 Study IV

In crude analyses, we found that higher parity increased breast cancer risk, using population controls, and, in particular, when using sister controls. In the adjusted analyses, there was inverse association between parity and breast cancer risk when population controls were used, whereas high parity was directly associated with an increased breast cancer risk when the sister controls were used (Table 9). Extreme prematurity was associated with higher risk, especially in comparison to the sister controls. A high maternal age at the last pregnancy was associated with a higher risk of premenopausal breast cancer, both when population and sister controls were used.

We found no noteworthy differences in the association between offspring birth weight, birth height, BW/GA and risk of premenopausal breast cancer when population and sister controls were used. A statistically significant inverse association was found between preeclampsia and risk of breast cancer risk using population controls, but not when using sister controls.

Two additional multivariable models that exclude GA or adjust for BMI and maternal height resulted in no noteworthy change in the associations between offspring characteristics and risk of breast cancer. In a sub-analysis, we found that a shorter maternal height and higher BMI in last pregnancy were associated with a lower risk of breast cancer using population controls, but not when using sister controls.

Table 9: Crude and adjusted Odds Ratio (OR) and 95% confidence interval (95% CI) for the association between parity and the risk of breast cancer in Swedish women diagnosed at the age 50 or younger during 1973-2010 in comparison to both population and sister controls.

	Cases of breast cancer Total n=8,349		Population controls Total n=1,053,688			Sister Control Total n=8,349		
	Number	Percent	Number	Percent	OR(95% CI)	Number	Percent	OR(95% CI)
Parity								
1	1444	17.3	196605	18.7	Referent	2779	33.3	Referent
2	4218	50.5	517930	49.2	1.10 (1.04-1.78)	3407	40.8	2.43 (2.24-2.63)
3	2068	24.8	249519	23.9	1.13 (1.06-1.21)	1598	19.1	2.59 (2.35-2.85)
≥4	619	7.4	89634	8.5	0.94 (0.86-1.03)	565	6.8	2.19 (1.90-2.52)
Parity [a]								
1	1,444	17.3	196605	18.7	Referent	2,779	33.3	Referent
2	4,218	50.5	517930	49.2	0.91 (0.86-0.97)	3,407	40.8	2.21 (2.03–2.40)
3	2,068	24.8	249519	23.9	0.76 (0.71-0.82)	1,598	19.1	2.13 (1.92–2.36)
≥4	619	7.4	89634	8.5	0.56 (0.51-0.62)	565	6.8	1.72 (1.48–2.00)

[a] Adjusted for maternal age at last pregnancy, parity, level of education and calendar year

6. Discussion

6.1 Methodological considerations

Epidemiology is defined as the study of the distribution and determinant of states and events in the human population, including health-related states and events (251). This definition encompasses not only disease and negative outcomes, but also physiological status such as blood pressure or reproductive status, as well as positive outcomes such as immunity or normal birth. The main aim of epidemiologic studies is to establish an accurate and valid estimation of the effects of some exposures on an outcome, using different approaches.

Epidemiological studies can be divided into two major groups: experimental investigations, including randomized controlled trials and quasi-experimental; and observational approaches consisting of case reports or case series, case-control, cohort, cross-sectional and ecological studies. Experimental studies involve comparison of at least a group subjected to the intervention (exposed) and another subjected (unexposed), in attempt to determine the impact of the intervention on the outcome(s) of interest. These groups are formed in a random and blinded fashion to reduce bias and confounding. In a single blinded trial, the participants receive no information about who is receiving the intervention; in a double-blinded trial neither the subjects nor researchers know; and in a triple-blinded the individuals who analyze the data do not know either.

Although experimental studies provide strong evidence of causality with low probability of bias, they are expensive and time-consuming. Nonetheless, the experimental approach (in humans, the Randomized Clinical Trial (RCT)) is considered the gold standard in epidemiological studies. For ethical reasons, humans can only be subjected to potentially beneficial interventions.

Non-experimental studies can help to avoid possible risks and achieve results of good accuracy. However, such studies are prone to a variety of potential biases or confounders.

6.1.1 Study designs

Non-experimental studies can be observational or analytical. Observational approaches include estimating the incidence or prevalence of a disease or the side effects of a drug or a surgical procedure. In one type of observational studies, referred to as ecological, data is collected on a group/community, but not on individuals; by comparing exposure, and outcomes at this level, a hypothesis can be created. In analytical studies, such as case-control

or cohort studies, the association between an exposure of interest and a particular outcome is estimated at the individual level.

6.1.1.1 Case-control design

Case-control studies begin by identifying cases and the study population should be defined exactly before case selection. All who fulfill the criteria for inclusion should be included. Cases can be identified from a registry, a vital record or a defined geographical area (population-based) or on the basis of information collected by hospitals or clinics (hospital-based). The controls should be representative of the community regarding the prevalence of exposure and should therefore be selected from the same population as the cases. Alternatively, when this is not possible, controls can be selected among relatives, neighbors or friends of the cases, although such groups might not be representative of the community.

Comparison of the odds of being exposed in the case and control groups is appropriate for rare diseases or for a disease with a long latency period. Case-control studies are less expensive and can be conducted in a shorter time than cohort studies, but are commonly prone to certain types of bias, such as recall or selection bias. Moreover, selecting a representative control group can be difficult.

Matching is one method for improving the validity and efficiency of this type of investigation. Matching makes cases and controls as similar as possible with regards to one or more characteristics/confounding factors, thereby controlling for important confounders. Matching can be done at the individual level, where one or more controls are matched with each case, or at the frequency level, where a group of controls is matched with a group of cases. In study three, we matched five controls to each patient with breast cancer on the individual level with respect to the year of birth, and also required the controls be alive at the time when their matched cases were diagnosed with breast cancer.

6.1.1.2 Nested-case control design

Nested-case control studies can be conducted when the cohort is well-defined, avoiding the issue of selection bias. Thus, with this approach, cases diagnosed during follow-up are included and one or more controls randomly selected at the time of diagnosis. Moreover, the probability of information bias is also low, because the information about exposure is collected before the outcome develops. A nested case-control study can be conducted when: a) more information is required after completion of data collection in a cohort study and collecting more data from all the study participants is expensive, b) when recollecting more data from all the cohort participants is technically impossible, or c) when performing a

particular procedure e.g., in the laboratory for an entire cohort population is expensive or even impossible for technical reasons.

In study three, we applied a nested case-control approach to a well-defined cohort of female twins of opposite-sexed twin pairs. We included all female twins diagnosed with breast cancer during the study period and for each case randomly selected five controls among female twins not diagnosed with breast cancer, employing matching with respect to the year of birth and requiring that the controls be alive at the date diagnosis of breast cancer in corresponding case.

6.1.1.3 Cohort design

A cohort study involves one group of individuals exposed to some factors of interest (the exposed group) and another not exposed group (the unexposed group). In this case, the subjects have not yet developed the outcome in focus and are monitored for this development. Comparing the occurrence of the outcome in both groups will provide the risk ratio for occurrence of this particular outcome due to the exposure of interest.

Cohort studies can be applied when the exposure of interest is rare or when you want to examine two or more outcomes. Subjects are selected and exposure status recorded before detection of the outcome. However, cohort studies are usually expensive, time-consuming, and inappropriate for rare outcomes. Lack of follow-up is also a concern here.

Studies one and two in the present thesis have cohort designs. In both cases, we individually linked information from existing data sources (registries). Since data was already collected, this was both an efficient and inexpensive procedure. In study one, placental weight from 1982 to 1989 was the main exposure (242) and in study two, the main exposure was birth weight (242). In both studies, the outcome was death due to all causes. We also utilized information about tumor characteristics from two regional quality registries of breast cancer in central Sweden covering a population of more than 4 million populations.

6.1.2 The validity of study

A causal association can be inferred by employing some criteria such as Hill's criteria of causal inference (252). Epidemiological estimation of an association should be valid and precise. Validity, defined as how closely we measured what we intended to, is of two types:

internal validity is violated by selection bias, information bias or confounding, while external validity concerns generalizability to other populations.

6.1.2.1 Internal validity

6.1.2.1.1 Selection bias

Selection bias, which arises from inappropriate selection of subjects or factors which influence participation (10), involves a differences between eligible participants in a study and those who are eligible but do not participate. This is a concern in connection with case-control studies. Cohort studies are less prone to selection bias, since subjects are selected on the basis of their exposure and prior to occurrence of the outcome.

In study one, we selected all parous women whose placental weight was available, and excluded women for whom such information was lacking. Given possible difference between eligible samples who were excluded and who were included in the study, we used multiple imputation method. We found no noteworthy difference between the two results.

In study three, we selected all female members of opposite-sexed twins diagnosed with breast cancer as cases and for each case, 5 female twins not diagnosed with breast cancer were selected as controls. In study four, we had two control groups, i.e., sister and population controls. Sisters with closest in age to the cases constituted the sister control group, while, the population controls were all women without breast cancer and not included in the sister control group.

6.1.2.1.2 Information bias

Information bias involves incorrect measurement of the exposure and/or outcome and usually leads to misclassification. Misclassification may be non-differential and differential. If the probability of being misclassified is the same for all classes or categories of a variable and for all subjects, it is referred to as non-differential misclassification. For example, measuring birth weight with a scale that is 100 grams off or categorizing esophageal cancer in subgroups which exhibit some overlap in diagnosis can be referred to as non-differential misclassification. Differential misclassification is based on the value of other study variables (253). When the probability of being misclassified is not the same for all classes or catergories of a variable and for all subjects, it is refered to as differential misclassification. For example, recall bias give rise to differential misclassification as explained below. Both

types of misclassifications can influence the results. Non-differential misclassification may lead to that differences will be diluted out and the results move toward no difference (null) if the exposure is dichotomous. If the exposure is categorical, the result may move towards or away from null, depending on which category was misclassified (253). In the case of differential misclassification, the result can move towards or away from null (253).

Recall bias occurs most frequently in case-control studies, when information on exposure is collected after the outcome: participants are asked to recall what had happened to them before occurrence of the outcome. If the accuracy of cases and controls in recalling events differs, a differential misclassification can be present. For example, when a mother of an affected offspring is asked to recall what happened before or during her pregnancy, she may remember more details about her pregnancy and its complications than a mother with an unaffected offspring. Since we collected the data on exposure before the occurrence on the outcome, recall bias was not a concern in our studies.

Imperfect measurement of exposure, outcome and/or potential confounding factors can also lead to information bias. In study one, placental weight was the main variable of interest in relationship to maternal risk of breast cancer mortality. Several factors can influence the measurement of placental weight, including time at which the umbilical cord is cut, and the scale used for weighing. Cutting the umbilical cord sooner or later after delivery influences how much blood remains in the placenta. Moreover, the length of the umbilical cord left after cutting can influence the weight of the placenta. Although guidelines for these procedures probably exist, these may vary between hospitals. The midwife doing the weighing and the scale used may also exert an impact on the weight obtained. This can lead to non-differential misclassification.

We employed placental weight and birth weight as indirect (proxy) indicators of estrogen levels during pregnancy. Proxies are likely to be influenced by a variety of other factors, thereby increasing the risk of misclassification. For example, placental weight is dependent on maternal size, size of the uterus, parity, weight gain during pregnancy, or diseases contracted during pregnancy, such as diabetes and hypertension. Offspring birth weight is dependent on genetic factors, maternal size, parity, gestational age and disease occurring during pregnancy, such as gestational diabetes or hypertension. Such factors may results in non-differential misclassification, especially if the proxies are considered to be categorical variables.

Another exposure which has been affected by measuring error is gestational age. Based on the time that elapsed between the first day of LMP and date of delivery, determination of GA may easily involve recall bias. Moreover, some cases of breast cancer might be missed or diagnosed incorrectly. The outcomes can be misclassified as well. In studies 1 and 2, the outcome of mortality due to all causes was checked in the Cause of Death Register and found to be about 99% complete.

6.1.2.1.3 Confounding

Confounding involves confusing or mixing up the effect of one exposure with the effect of another variable (253). Confounders are risk factor for the outcome, associated with the exposure and not an intermediate between the exposure and outcome. A confounder can lead to overestimation or underestimation of an association or even alter its nature, e.g., from positive to negative.

In studies 1 and 2, the potential confounders were GA, parity, age at diagnosis and level of education, which we adjusted for in our models. Nonetheless, there might have been some residual confounding. In examining a potential association between placental weight or birth weight and breast cancer mortality, we also performed analyses restricted to different subcategories of tumor characteristics to control for potential confounding by tumor characteristics. Since we did not have information about smoking and diseases during pregnancy, such as hypertension or diabetes, these factors could not be taken into account.

In study 3, we used different models to estimate the association between breast cancer risk and offspring birth weight in opposite-sexed twins and also matched cases and controls with respect to their year of birth. In one model, we adjusted for GA; the second adjusted for GA, maternal age, parity, and hypertensive disease during pregnancy; and third adjusted for all the same variables as in the second model plus socioeconomic status.

In study four, we adjusted our models for maternal age at last pregnancy, parity, level of education, calendar year and gestational age. We also performed an additional analysis with adjustment for GA.

6.1.2.1.4 Random error or chance

Although the possibility of random error, i.e., what remains after elimination of systematic error (253), cannot be totally excluded, statistical procedures can be applied to estimate the role played by chance in the results. Observed determination of the P-value (i.e., the probability of the occurrence of a result as extreme as or more extreme than if the null hypothesis is true) is one such approach. More informative is to estimation of the confidence interval (CI), i.e., a range of values which contain the true measure with 95% probability. Random error is related to the precision of the study. The most effective way to deal with random error is by increasing sample size, thereby decreasing such random error and increasing the precision and power of the study.

The studies described in this thesis involved relatively large populations and, as we calculated, reasonable statistical power for estimation of the main association. However, stratified analyses reduced the number of subjects in certain subcategories, thereby reducing statistical power. In study one, the sample size for estimating the association between maternal risk of mortality and placental weight in relation to subcategories of tumor characteristics was small. Therefore, we divided the tumors into three stages instead of four. In study 2, the numbers of events in certain subcategories, e.g., ER/PR subgroups were small. Studies 3 and 4 were large, and limited statistical power was not an issue.

6.1.2.2 External validity (generalizability)

External validity or generalizability, i.e., the possibility of extending the results of an investigation to a larger population, depends (assuming internal validity) on various factors, including biological interaction. Study 3 involved twins and there might be differences between twins and singletons that could influence the finding obtained. For example, twins exhibit a different pattern of growth during pregnancy (254) and have less physical space in the uterus. Moreover, twins and singletons appear to differ with respect to subsequent diseases in adulthood (255-257). Accordingly, the generalizability of the results of study 3 still can be questioned. However, most studies suggested that there is no difference between twins and singeltons.

6.1.3 General discussion

This thesis includes four epidemiological studies investigating associations between indirect indicators of pregnancy hormone exposure and breast cancer risk and survival, with special emphasis on young breast cancer patients.

In the first study, we found an association between placental weight and maternal risk of mortality from breast cancer which was more pronounced among women with ER-/PR- tumor receptive status. Previously, investigators have suggested that breast cancer tumors should be categorized on the basis of their expression of both ERs and PRs, rather than individual expression (207). ER-/PR- tumors are more frequent in premenopausal breast cancer, whereas in postmenopausal breast cancer ER+/PR+ tumors are more frequent (71, 207, 258, 259). In addition, ER-/PR- tumors demonstrate higher proliferation rate (197, 258, 260), more advanced stage (71, 207, 258), and higher proportion of cells in S-phase (260, 261).

The expression of receptors is more dependent on age (71, 204, 205, 208, 229, 262-264) than on menopausal status. In fact, the incidence of ER- breast cancer increases with age during the premenopausal period, reaching a constant level after 50 years of age; while the greatest incidence of ER+ tumors occur after 70 years (204, 208). Certain reports document statistically significant higher frequency of ER-/ PR- tumors among cases of pregnancy-related breast cancers (163, 166). Therefore, it can be suggested that premenopausal hormonal exposure exerts a greater impact on receptor-negative than on receptor-positive tumors. However, the biological mechanisms underlying the elevated breast cancer mortality risk observed among patients with ER-/PR- tumors and higher placental weight remain to be explained.

The findings of study one is consistent with previous findings (42, 71, 189, 201, 228, 240, 265) that breast cancer mortality among premenopausal women with ER-/PR- tumors is higher than for those with ER+/PR+ tumors. Dunnwald and colleagues (228) observed that premenopausal women with ER+/PR-, ER-/PR+, or ER-/PR- tumors all experienced higher risks for breast cancer mortality than those women with ER+/PR+ tumors. These differences were largely independent of demographic and clinical tumor characteristics, and ER-/PR- tumors conferred the highest risk. Examining ER+/PR- and ER-/PR+ tumors can be problematic due to their low incidence (71, 207, 231, 259). It has been proposed that estrogen and ERs are required for the synthesis of PRs, and that identification of ER-/PR+ tumors

may be laboratory mistake (266). In addition, receptor-positive tumors can become receptor-negative with time (267).

Lukanova and co-workers (108) reported that higher levels of estrogen during the first trimester was associated with an enhanced risk of breast cancer, and also reported a higher proportion of receptor-negative tumors among women diagnosed before the age of 40, observations consistent with our own results. Animal experiments showing that even ER- breast cancer tumors require estrogen for their formation and progression (238) have led to speculation about a direct association between estrogen levels and such tumors. However, in certain other investigations (268) there was no clear association between estrogen levels in the third trimester of pregnancy and risk of breast cancer. In addition, a recent large cohort study did not find any association between placental weight and breast cancer risk (269).

In the second study, we observed no association between birth weight and risk of premenopausal breast cancer mortality, not even when taking tumor characteristics into consideration. These findings are not consistent with those of the first study, where high placental weight was associated with increased risk, an association which was modified by tumor characteristics. The placenta is the primary source of pregnancy hormones and placental weight might be a more robust and independent indicator of hormone exposures during pregnancy than birth weight (270), which could explain these inconsistencies. In another investigation, the effect of offspring's birth weight on mother's risk of premenopausal breast cancer disappeared after adjusting for placental weight (36).

In addition, birth and/or placental weight could be markers for other exposure(s) that might influence cancer mortality. For example, a disproportionately large placenta might reflect the presence of a chronic process requiring placental overgrowth, such as maternal anemia or malnutrition (271), but whether this would influence breast cancer mortality is unknown. Moreover, our finding of enhanced maternal risk of mortality among those giving birth to small-for-gestational age offspring was restricted to uniparous women. We speculate that this finding might be due to comorbidities in the mother, such as autoimmune diseases (272, 273), or to other risk factors such as cigarette smoking (274), which could affect both offspring birth weight and mortality.

The third study revealed no association between birth weight and the risk of pre- or postmenopausal breast cancer among the female members of opposite-sexed twins, a finding consistent with several earlier cohort (87, 88, 90) and case-control studies (65, 66, 89, 275-278). However, many investigations, including two recent meta-analyses (75, 279) and a re-

analysis of 32 previous studies (76) conclude that a high birth weight is associated with a modestly increased risk of breast cancer (77, 78, 80, 81, 86, 280), but the association may be restricted to premenopausal breast cancer (77, 80-86, 280). However, many published studies suffer from a limited sample size. Among women with high birth weight, we also observed a more than 1.7% increased risk of premenopausal breast cancer, but this effect is not statistically significant.

There is only one other investigation on the potential association between birth weight and breast cancer risk in opposite-sexed twins (73). Kaijser and colleagues (73) found that the risk of breast cancer was 12-fold higher among female twins with a birth weight of more than 3,500 grams than among those whose birth weight was 2,000 grams or less. However, the sample size was small (only 90 breast cancer cases) and study period was relatively short.

In two other Swedish twin studies, the potential association between birth weight and breast cancer risk within like-sexed twin pairs was examined. In the small case-control study, a non-significantly higher risk was present among the twins with the higher birth weight (276); while in the larger, more recent investigation, this difference was on statistically significant for premenopausal breast cancer (85). Our birth cohort was of wider range (1926-1972) and the study period longer (1972-2008) than in these two studies of like-sexed twins. Since a statistically significant positive association between birth weight and premenopausal breast cancer was observed in the larger study of like-sexed twins (85) but not by us, we speculate that prenatal exposure to androgens may also be important for breast cancer risk. However, we observed no effect of male co-twins birth weight (possibly also reflecting prenatal exposure to androgens). The interactions between maternal, placental and fetal steroid production and exchange are complex and not completely understood (281).

In the fourth study, multiparous women demonstrated a higher risk of premenopausal breast cancer than uniparous women when the sister controls were used for analysis. In contrast, when population controls were used, this association was the inverse, suggesting a gene-environmental interaction. These findings are consistent with previous reports (282-285). One previous study report that higher parity is associated with an increased risk of premenopausal breast cancer when sister controls are used, but not when population controls are used (283). Another case-control study (282) demonstrated that the protective effect of parity was present among women without a family history of breast cancer but not among women with such a family history and that parity interacted with genetic effects.

Very preterm delivery was associated with a higher breast cancer risk, and to a greater extent using sister than population controls. This result is consistent with previous finding of higher risk of breast cancer among mothers who delivered at lower gestational age (59, 60). Another investigation (59) has reported that the risk of breast cancer was two times higher among those with very preterm delivery than those delivering after 36 weeks of pregnancy. In addition, Melbye and co-workers (60) showed that among women younger than 50 years, the risk of breast cancer was 72% higher for those who had ever delivered at 31 weeks of gestational age or earlier than for other parous women.

One hypothesis in this context is that since mammillary cells proliferated during the first and second trimesters of pregnancy and differentiate during the third, shortening pregnancy maintains the proliferation of these cells, which might increase the risk of breast cancer (61). The higher risk of premenopausal breast cancer observed using sister controls suggests a gene-environmental interaction, i.e., a different effect of parity or a related factor on the risk of premenopausal breast cancer in women with different genotypes.

The association between risk of premenopausal breast cancer and maternal characteristics, including maternal age at last pregnancy and BMI, were not confounded by familial factors. Higher maternal age at last pregnancy was associated with an increased risk of premenopausal breast cancer in both control groups, which is consistent with most previous findings (39, 286), but not all (287). There was inverse association between maternal BMI in the last pregnancy and the risk of premenopausal breast cancer, which is also consistent with previous reports (36, 48, 49).

7. Conclusion

- Our findings provide some support for the hypothesis that hormone levels during pregnancy influence premenopausal breast cancer mortality, and that this association is influenced by tumor receptor status.

  The increased risk of mortality from ER-/PR- tumors associated with higher placental weight suggests that premenopausal hormonal exposure might exert a greater impact on such tumors.

- The hypothesis that ‘‘premenopausal breast cancer mortality is associated with offspring birth characteristics in connection with the most recent pregnancy before diagnosis’’ may not be true. In addition, any such association is not modified by tumor characteristics.

- Higher offspring birth weight is not associated with offspring’s subsequent risk of breast cancer.

  The association between birth weight and risk of breast cancer is not influenced by the birth weight of the male co-twins.

- The association between parity and gestational age and risk of premenopausal breast cancer may be influenced by a gene-environment interaction.

- The association between other reproductive factors and risk of premenopausal breast cancer was not confounded by familial factors

8. Final remarks and future perspectives

Breast cancer is the leading form of cancer among women world-wide, and identification of risk and prognostic factors could be of enormous value in improving the prevention and treatment of this disease. The present thesis has tried to answer some relevant questions, but several new questions have also been raised. Future studies should include the following:

- Performing a study with much bigger sample size investigating the potential association between placental weight and mortality from premenopausal breast cancer.

- Employing the st. Gallen classification method to determine whether the association between premenopausal breast cancer mortality and reproductive factors is influenced by tumor characteristics.

- The higher risk of maternal mortality from breast cancer observed in association with very preterm delivery in study two should be explored in more detail on a larger population.

- The main focus here was on premenopausal breast cancer and postmenopausal breast cancer deserves similar attention.

- In light of the more rapidly increasing and higher rate of mortality from breast cancer in low-income countries, analogous studies should be performed in these areas.

Studies which needs collaboration with other research groups:

- Many reproductive factors are associated with breast cancer risk and mortality but the underlying mechanism(s) remain to be elucidated.

- The associations with certain risk factors (e.g. placental weight) only in specific subgroups of tumors observed here should be confirmed using a larger population and the underlying mechanism(s) unraveled.

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