

Breast Cancer May Originate In Utero: The Importance of the Intrauterine Environment for Breast Cancer Development

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3.1 Introduction

Breast cancer is the most common female cancer worldwide and the second leading cause of cancer death (after lung cancer) (American Cancer Society 2009). The incidence of breast cancer varies four- to fivefold across countries, is the highest in Europe and North America, and the lowest in Asia (Ferlay et al. 2001). Breast cancer incidence has been on the rise since the 1930s, with more dramatic increase in the 1980s (White et al. 1990; Devesa et al. 1994). The incidence of breast cancer in the US stabilized from 2001 to 2003 and started to decline in 2003, possibly due, in part, to the reduced use of hormone replacement therapy (Howe et al. 2006). It was projected that in 2010, 207,090 women would develop invasive breast cancer and 39,840 women will die from the disease (American Cancer Society 2010).

Through decades of research, factors including family history of breast cancer in first-degree relatives, benign breast disease, mammographic density, endogenous hormone levels, younger age at menarche, low parity, older age at first birth, older age at menopause, postmenopausal hormone use, ionizing radiation exposure, height, high postmenopausal body mass index, and low premenopausal body mass index have been established as risk factors of breast cancer (Adami et al.

2002). Nonetheless, only a modest percentage of breast cancer cases are attributable to recognized risk factors (Madigan et al. 1995), and most epidemiologic investigations of the etiology of breast cancer have concentrated on events during women's reproductive years. To provide an alternative perspective on the etiology of breast cancer, this chapter reviews evidence supporting the effect of intrauterine exposures on breast cancer development and discusses potential underlying mechanisms including alterations in levels of pregnancy steroid hormones and growth factors and their impact on prenatal development of mammary stem cells.

3.2 Intrauterine Exposure and Breast Cancer Risk

In an early animal experiment, 19 out of 23 female pregnant rats (82.6%) injected with carcinogenic agents (dibenzanthracene in olive oil) through the uterine wall directly into amniotic fluid had offspring which developed primary carcinoma of the lung (Law 1940). Other animal studies have also suggested that when pregnant animals were exposed to any of at least 38 different chemical carcinogens, the offspring were more likely to develop tumors (Tomatis 1979). In parallel with findings from animals, descendants of women who were exposed to carcinogens such as diethylstilbestrol (DES) were reported to have increased risk of vaginal adenocarcinoma (Greenwald et al. 1971). Additionally, intrauterine exposure to ionizing radiation was found to be related to leukemia and other tumors in childhood (Macmahon 1962).

Based on evidence from early animal and human studies, Trichopoulos hypothesized that exposure to high levels of endogenous estrogens in utero might

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initiate breast cancer development, and that perinatal factors might be used as surrogate measures of intrauterine estrogen exposure (Trichopoulos 1990a, b). Subsequently, numerous epidemiologic studies have been conducted on various potential measures of intrauterine exposure, including birth weight and other measures of birth size, parental age at delivery, gestational age, twin membership, radiation, and other pregnancy-related complications and maternal characteristics (Xue and Michels 2007a).

3.2.1 Birth Weight

As a potential marker of intrauterine exposure to insulin-like growth factor (IGF)-I (Bennett et al. 1983; Reece et al. 1994), IGF-II (Bennett et al. 1983; Reece et al. 1994; Baldwin et al. 1993; Hill 1990), and estrogen (Petridou et al. 1990; Liehr 2000), birth weight is the most studied intrauterine factor in the context of breast cancer. More than 30 publications have collectively suggested that higher birth weight is associated with around 15–25% increased risk of breast cancer relative to low birth weight (Michels and Xue 2006; Xue and Michels 2007a; Park et al. 2008; Xu et al. 2009). The thresholds usually identified were >4,000 g for high birth weight and <2,500 g for low birth weight. Results from a recent pooled analysis including 21,825 breast cancer cases from 29 studies on birth size and the risk of breast cancer also suggested that, relative to birth weight of 3,000–3,499 g, those weighing $\geq 4,000$ g had a higher risk of breast cancer [Relative risk (RR)=1.12, 95% CI 1.00–1.25] (Dos Silva et al. 2008). When breast cancer cases were separately assessed according to menopausal status, premenopausal cancer was more consistently associated with the risk of breast cancer than postmenopausal breast cancer (Michels and Xue 2006). The association persists across various study designs (case-control or cohort), method of birth weight assessment (birth records, self-reports, reports by the mother, etc.), and different countries. Furthermore, the association between birth weight and the risk of breast cancer does not seem to be confounded by other measured intrauterine factors, such as gestational age, birth length, maternal preeclampsia or eclampsia, parental age, birth order, parental smoking, or multifetal gestation, etc. (Michels and Xue 2006).

3.2.2 Maternal Age at Delivery

Women who give birth at older age have higher serum estrogen levels possibly exposing the fetus to elevated levels of this hormone (Petridou et al. 1990; Panagiotopoulou et al. 1990). At least 16 studies have evaluated the potential influence of maternal age at delivery on the risk of breast cancer among daughters (Xue et al. 2006; Park et al. 2008; Nichols et al. 2008). Results from the majority of studies which assessed this association regardless of the menopausal status at diagnosis suggest an increased risk of breast cancer associated with older maternal age at birth (Xue and Michels 2007a; Park et al. 2008). A meta-analysis has suggested a statistically significant 13% increase in breast cancer risk associated with older maternal age, and the association holds for both cohort and case-control studies. The cutoff point of high maternal age varied from late twenties to late thirties. Results did not differ materially between pre- and postmenopausal breast cancer (Xue and Michels 2007a). Several studies considered paternal age and birth order, both of which may be correlated with maternal age, as potential confounders. Adjustment for paternal age produced varying effects: the association was attenuated in several studies (Le Marchand et al. 1988; Zhang et al. 1995; Hemminki and Kyronen 1999; Xue et al. 2006) but persisted in others (Janerich et al. 1989; Innes et al. 2000; Choi et al. 2005). Birth order was less influential and the maternal age-breast cancer association remained essentially the same in almost all studies that adjusted for it in the analysis (Xue and Michels 2007a).

3.2.3 Paternal Age at Delivery

Children born to older fathers have a higher incidence of autosomal dominant disorders, which have been related to increased base substitutions and structural chromosomal anomalies in spermatozoa (Jung et al. 2003; Glaser and Jabs 2004). Meiosis errors are also expected to be more prevalent in paternal than maternal germline with increased age, since sperm cells continued to divide after birth, unlike egg cells (Jung et al. 2003). Furthermore, DNA-repair activity and apoptosis of germ cells in response to mutagens were found to decline with paternal age (Wei et al. 1993;

Brinkworth 2000). At least 11 studies have examined older paternal age as a potential risk factor for breast cancer among daughters (Xue and Michels 2007a; Weiss-Salz et al. 2007), and findings from these studies have collectively suggested an approximate 10% increase in the risk of breast cancer associated with older paternal age at birth (the cutoff point ranged from early to late thirties). Studies that separately assessed premenopausal breast cancer collectively suggested a slightly stronger association with older paternal age (Xue and Michels 2007a; Weiss-Salz et al. 2007), though no study has separately evaluated postmenopausal breast cancer. After adjustment for maternal age as a potential confounding variable, the paternal age-breast cancer association persisted with statistical significance in two (Janerich et al. 1989; Choi et al. 2005) out of eight studies (Le Marchand et al. 1988; Janerich et al. 1989; Zhang et al. 1995; Hemminki and Kyyronen 1999; Innes et al. 2000; Hodgson et al. 2004; Choi et al. 2005; Xue et al. 2006), despite the potential collinearity between maternal and paternal age. Similar to studies on maternal age, most studies on paternal age adjusted for birth order as a potential confounding variable, and results remained essentially unchanged (Xue and Michels 2007a).

3.2.4 Birth Order

Pregnancy estrogen is higher for the first pregnancy than the second or later pregnancies (Panagiotopoulou et al. 1990). Levels of estradiol, estrone, and progesterone are also higher during the first pregnancy and decrease in subsequent pregnancies (Maccoby et al. 1979). Thus, in utero exposure to pregnancy hormones may be higher for a fetus of a primipara than a subsequent conception. A meta-analysis on the association between birth order and the risk of breast cancer included 17 published studies including 15 case-control and 2 cohort studies (Park et al. 2008). Among 14 studies which compared first births with 2nd or higher birth order, the risk of breast cancer in adulthood did not differ (summary RR=0.97, 95% CI 0.91–1.04) across all studies or among case-control studies (OR=0.99, 95% CI 0.94–1.04), though the one single cohort study reported a decreased risk for first birth (OR=0.28, 95% CI 0.21–0.36). When higher birth orders were studied,

birth orders 2–4 did not differ in risk (OR=0.97, 95% CI 0.91–1.03), but women with a birth order of 5+ were at a marginal reduced risk (OR=0.88, 95% CI 0.75–1.01) relative to first birth. A recent case-control study suggested that breast-feeding status in infancy may modify the association between birth order and breast cancer as birth order was inversely associated with breast cancer only among breast-fed women (Nichols et al. 2008).

3.2.5 Gestational Age

Gestational age has also been suggested to be related to the risk of breast cancer, mainly because hypothalamic maturation in utero, which is closely related to the length of gestation, determines the level of postnatal gonadotropin. In fact, during the first 10 weeks after birth, daughters born with a shorter gestational age have substantially higher levels of gonadotropins (Tapanainen et al. 1981), which may lead to ovarian hyperstimulation and consequently elevated estradiol levels and breast cancer risk (Ekbom et al. 2000). Furthermore, girls who survive preterm birth are likely to experience an accelerated postnatal growth which has been suggested to be associated with a higher risk of breast cancer later in life (Forman et al. 2005). The effect of gestational age on the risk of breast cancer has been assessed in at least 12 studies to date (Xue and Michels 2007a; Park et al. 2008). Despite the biological plausibility, these studies generated fairly mixed results with regard to both the direction and the significance of the association. The cutoff point for shorter gestational age used in the reviewed studies ranged from ≤ 32 weeks to < 39 weeks, and for longer gestational age ≥ 35 weeks to ≥ 42 weeks. Meta-analyses based on these studies suggested a lack of significant association between gestational age or preterm birth and breast cancer (Xue and Michels 2007a; Park et al. 2008). When premenopausal breast cancer and postmenopausal breast cancer were separately assessed, neither was significantly associated with breast cancer risk. The results were also consistent across cohort and case-control studies. Adjustment for birth weight, birth order, family history of breast cancer and other early-life factors had minimal influence on the effect estimates for gestational age (Xue and Michels 2007a).

3.2.6 Birth Length

As a strong correlate of birth weight, birth length may affect the risk of breast cancer through the same underlying mechanisms, e.g., increased intrauterine exposure to estrogen, IGF-1, and IGF-II. Indeed, birth length was found to be positively related to estrogen levels in maternal blood (Troisi et al. 2003a; Mucci et al. 2003). To date, the association between birth length and the risk of breast cancer has been evaluated in at least eight published studies. A meta-analysis of these studies has suggested an approximate 28% (95% CI 11–48%) increased risk comparing higher birth length (cutoff point ≥ 49 to ≥ 53 cm) to lower birth length (cutoff point ≤ 44 to < 50 cm) (Xue and Michels 2007a). Additionally, a recent pooled analysis involving 3,612 cases from 11 published and unpublished studies reported a significant 17% (95% CI 2–35%) increase in the risk of breast cancer for women with birth length ≥ 51 cm relative to those with birth length < 49 cm (dos Silva et al. 2008). In the two studies that separately evaluated premenopausal breast cancer and postmenopausal breast cancer, the association of birth length with premenopausal breast cancer was more consistent than that with postmenopausal breast cancer (McCormack et al. 2003; Vatten et al. 2005). Other birth size measures, e.g., birth weight and head circumference, are likely confounders for the birth-length breast cancer association. However, these factors did not completely account for the observed association between birth length and breast cancer risk (McCormack et al. 2003).

3.2.7 Diethylstilbestrol (DES)

From 1938 through 1971, DES, a synthetic estrogen, was used in the US to support pregnancies which were threatened by miscarriage or premature birth. Adolescents exposed to DES before birth were found to have an elevated risk of vaginal adenocarcinoma (Greenwald et al. 1971). This observation suggested that cancer may originate in utero. Trichopoulos later hypothesized that prenatal exposure to high levels of estrogen may increase breast cancer risk later in life (Trichopoulos 1990a, b). To date, the association

between DES and breast cancer risk has been examined in at least five studies (Weiss et al. 1997; Hatch et al. 1998; Sanderson et al. 1998; Palmer et al. 2002; Troisi et al. 2007), and two of these studies (Hatch et al. 1998; Palmer et al. 2002) were updated by more recent analyses. Only one of the remaining three studies assessed breast cancer overall (RR = 1.40, 95% CI 0.86–2.28) and premenopausal breast cancer (RR = 1.87, 95% CI 0.72–4.83) comparing women with prenatal exposure to DES to those without it (Palmer et al. 2002). A meta-analysis of the remaining three studies on postmenopausal breast cancer produced a summary RR of 1.37 (95% CI 0.86–2.18) for women with prenatal exposure to DES (Xue and Michels 2007a). When other early-life exposure variables including gestational age at first DES exposure were adjusted for as potential confounders, the association remained essentially unchanged (Hatch et al. 1998).

3.2.8 Twin Membership

Compared with singleton pregnancies, twins can elicit almost twice the level of pregnancy-related hormones, including estrogen (TambyRaja and Ratnam 1981; Gonzalez et al. 1989), gonadotropin, and lactogen (Thiery et al. 1977). Furthermore, dizygotic twins may elicit a higher level of pregnancy-related hormones than monozygotic twins because they have two placentas (Kappel et al. 1985). Conversely, because multiple pregnancy likely induces earlier termination of pregnancy due to pregnancy-related complications, twins may experience shorter intrauterine exposure to pregnancy hormones than singletons. Despite conflicting results on the association between gestational age and the risk of breast cancer from existing studies, it is biologically plausible that longer duration of intrauterine exposure to pregnancy hormones may increase the risk of breast cancer later in life. At least 14 studies have investigated the association between twin membership and the risk of breast cancer (Xue and Michels 2007a; Park et al. 2008). Regardless of the menopausal status of breast cancer cases, these studies suggest a decrease in risk of about 7% in twins (marginal statistical significance) compared with singletons. When premenopausal and postmenopausal breast cancer cases were

separately examined, the direction of the association was similar to the combined analysis (Xue and Michels 2007a). Interestingly, when monozygotic twins and dizygotic twins were separately assessed, dizygotic twin membership was associated with a marginally increased risk of breast cancer, though results from the included studies were heterogeneous; monozygotic twin membership was associated with a decreased risk (Xue and Michels 2007a). These results suggest that the extra pregnancy hormone secretion due to the two placentas in dizygotic twins may overpower the reduced duration of exposure due to early termination of pregnancy. Dizygotic twins are also more often conceived by women who are taller or overweight, older, or non-Hispanic blacks, factors that may also differentiate their risk profile of breast cancer from that of monozygotic twins (Shipley et al. 1967; Oleszczuk et al. 2001; Hamilton et al. 2006). Nonetheless, more data are needed to confirm these hypotheses, particularly because studies that directly assessed the effect of zygosity of twin membership on breast cancer risk by comparing dizygotic twins to monozygotic twins (Swerdlow et al. 1997) or opposite-sex twins to same-sex twins (Swerdlow et al. 1996) did not suggest any significant difference.

3.2.9 Preeclampsia and Eclampsia

Preeclampsia and eclampsia are characterized by pregnancy-related hypertension and edema, with or without seizure, respectively. It has been suggested that pregnant women with preeclampsia or eclampsia have lower estrogen levels in blood (Zeisler et al. 2002) and urine (Long et al. 1979) than those without these disorders. Furthermore, preeclampsia and eclampsia may induce early termination of pregnancy because they are related to increased maternal and fetal morbidity and mortality, especially during the third trimester. Daughters born to mothers with preeclampsia or eclampsia are thus expected to have a decreased risk of breast cancer due to a reduced cumulative intrauterine exposure to estrogen and other pregnancy hormones than those born after normal pregnancy. To date, the effect of preeclampsia or eclampsia on the risk of breast cancer has been investigated in at least six studies, and a meta-analysis has suggested that preeclampsia or eclampsia is associated with a substantially

lower (52%) risk of breast cancer relative to normal pregnancy, though effect estimates from included studies were heterogeneous (Xue and Michels 2007a). Multiple pregnancy and maternal anthropometric factors prior to pregnancy may confound this association, but have not been considered in the studies available.

3.2.10 Other Intrauterine Exposures

Besides the aforementioned intrauterine factors or markers of intrauterine exposure that have been extensively studied, several other factors have also been suggested to be related to breast cancer risk, though the evidence is still sparse. Much has been learned from the bombing of Hiroshima and Nagasaki about the influence of intrauterine exposure to ionizing radiation on subsequent cancer risk. Children exposed to the atomic bombings in utero were at a higher risk of cancer overall, especially cancer in childhood, compared to children whose mothers were not exposed (Kato et al. 1989). Additionally, though intrauterine data were not reported, the relative risk associated with exposure to the atomic bomb blasts was the highest among the group who were youngest when exposed (0–5 years) (Land 1995).

Several perinatal conditions have also been studied in relation to subsequent risk of breast cancer, though the evidence is still insufficient to draw any conclusions. Neonatal jaundice is a potential marker for infection in utero or impaired fetal liver function, which increases endogenous estrogen levels (Lauritzen and Lehmann 1966; Robine et al. 1988). One study that assessed neonatal jaundice in relation to the risk of breast cancer later in life suggested a significant doubled risk among infants with neonatal jaundice compared to those without it (Ekbom et al. 1997). Maternal gestational diabetes has also been suggested to influence fetal growth through altering placental growth hormone levels, which may modify substrate availability and regulate paracrine actions in the placental bed (McIntyre et al. 2009). Maternal gestational diabetes was studied as a risk factor for breast cancer among daughters in one study, which found no association (Mogren et al. 1999). Maternal weight gain during pregnancy was positively associated with the risk of breast cancer in daughters in the one study considering this association [OR 1.5 (95%

CI 1.1–2.1) for a gain of 11–15 kg relative to a gain of <7 kg] (Sanderson et al. 1998). Maternal life style factors during pregnancy, e.g., coffee consumption and alcohol consumption, were not related to the daughter's breast cancer risk (Sanderson et al. 1998).

3.2.11 Summary of Evidence

A summary of the existing evidence regarding a range of intrauterine exposure variables in association with the risk of breast cancer is displayed in Table 3.1.

Table 3.1 Summary of evidence for intrauterine exposures and the risk of breast cancer

Intrauterine exposures	Direction of association	Strength of the evidence
Higher birth weight	↑	+++
Advanced maternal age at delivery	↑	++
Advanced paternal age at delivery	↑	++
Higher birth order	∅	+
Longer gestational age	∅	±
Higher birth length	↑	++
DES exposure	∅	±
Twin membership overall	↓	+
Monozygotic	↓	+
Dizygotic	↑	+
Preeclampsia and eclampsia	↓	++
Other intrauterine factors		
Ionizing radiation	↑	++
Neonatal jaundice	↑	±
Maternal diabetes	∅	±
Maternal weight gain during pregnancy	↑	±
Maternal coffee consumption	∅	±
Maternal alcohol consumption	∅	±

↑, increased risk of breast cancer; ↓, decreased risk of breast cancer; ∅, no association

+++ , likely association; ++, probable association; +, possible association; ±, evidence is too sparse to draw any conclusion

3.3 Potential Mechanisms

As mentioned for each of the intrauterine exposures, the majority of the mechanisms underlying the association between these exposures and the risk of breast cancer likely involve alterations of maternal pregnancy hormones, growth hormones, and IGFs, as well as consequent mammary stem cell abnormalities.

3.3.1 Hormone Alterations

3.3.1.1 Estrogen

Intrauterine exposure to elevated endogenous estrogen levels was the basis of the initial hypothesis raised by Trichopoulos (1990a, b). Birth weight, maternal age, gestational age, birth length, twin membership, preeclampsia, and eclampsia all affect intrauterine estrogen levels and possibly subsequent breast cancer risk.

From the fourth week to the seventh week of gestation, the placenta supplants the maternal ovaries as the main source of estrogen in both the maternal and fetal circulation (Siiteri and MacDonald 1966; Csapo et al. 1973). By the end of gestation, maternal estriol production is 1,000 times the average daily level in normal ovulatory women, and it becomes the most important estrogen in pregnancy (Tulchinsky et al. 1971). Additionally, estradiol and estrone also increase in maternal blood and rise from 50–100 pg/ml to 30,000 pg/ml at term (Lindberg et al. 1974). On the fetus's side, by the end of the third trimester, around 90% of estriol is produced by placenta from 16 α -hydroxydehydroepiandrosterone sulfate in fetal plasma, and 50% of estradiol is produced by placenta from fetal dehydroepiandrosterone sulfate (DHEAS). The majority of these steroid hormones (80–90%) from the placenta enter the maternal circulation (Casey and MacDonald 1992). Thus, the level of DHEAS production by fetal adrenal glands determines the level of circulating estrogens in both maternal and fetal blood. Fetal and maternal hormone levels were found to be correlated, with correlation coefficient of 0.26, 0.27, and 0.41 for estriol, estradiol, and estrone, respectively (Troisi et al. 2003b).

Estrogen has long been recognized as a promoter of cancer growth due to its growth-stimulating potential. It was believed that estrogen would stimulate cell proliferation and cell growth and promote cancer development by increasing the chances that a cell with potential cancer-causing mutations will multiply, while the initiation of the mutation was attributed to other internal or external carcinogens (Pike et al. 1993; Platet et al. 2004). Later studies based on cell culture suggested that estrogen metabolites can bind to DNA and trigger mutations; estrogen metabolites may also influence the levels of enzymes involved in the removal of active compounds such as 4-hydroxyestradiol that might initiate cancer (Zhu and Conney 1998). These data suggest that estrogen may also be a cancer initiator (Service 1998).

3.3.1.2 Insulin-Like Growth Factors (IGFs)

IGFs are 7-kDa polypeptides structurally homologous to proinsulin, synthesized by almost all tissues but mainly by liver in humans (Le Roith 1997; Zapf et al. 1984). They are important mediators in regulating cell growth, differentiation, and transformation (Le Roith 1997). Both *IGF1* and *IGF2* genes are expressed in fetal tissues throughout gestation and play important roles in the regulation of fetal-placental growth (Fowden 2003). IGF-I and IGF-II stimulate cell division and differentiation through autocrine, paracrine, and endocrine means during gestation (Ostlund et al. 2002). Fetal serum levels of IGF-I and IGF-II increase with gestational age (Giudice et al. 1995).

In humans, partial *IGF1* deletion has been linked to severe intrauterine growth failure (Morison et al. 1996). Studies have consistently shown that IGF-I levels in fetal blood are positively related to indicators of birth size, including birth weight (Gluckman et al. 1983; Osorio et al. 1996; Klauwer et al. 1997), birth weight independent of gestational age (Gluckman et al. 1983; Lassarre et al. 1991), birth length (Klauwer et al. 1997), ponderal index (Osorio et al. 1996), and placental weight (Osorio et al. 1996). Spencer et al. found that infants who were small for gestational age according to the first ultrasound measurement, with evidence of subsequent fetal growth restriction, had significantly lower cord blood IGF-I than did infants who were small for gestational age but with normal

subsequent growth and infants appropriate for gestational age (Spencer et al. 1995).

The importance of IGF-II in determining intrauterine growth is less consistently supported by human studies that link fetal blood IGF-II level to birth size. In a study by Giudice et al., IGF-II in fetal cord serum was significantly lower in infants with intrauterine growth retardation (Giudice et al. 1995). Ong et al. found that fetal circulating IGF-II was weakly correlated to ponderal index at birth ($r=0.18$) and placental weight ($r=0.18$) (Ong et al. 2000). Bennett et al. also found a significant positive correlation between birth weight and cord IGF-II level (Bennett et al. 1983). However, other studies failed to confirm the association of fetal IGF-II level with measures of birth size, including birth weight (Gluckman et al. 1983; Lassarre et al. 1991; Osorio et al. 1996; Klauwer et al. 1997), birth weight independent of gestational age (Gluckman et al. 1983), birth length (Klauwer et al. 1997), ponderal index (Osorio et al. 1996), and placental weight (Osorio et al. 1996) possibly because IGF-II levels measured at birth do not reflect levels throughout pregnancy. The importance of IGF-II is greatest during intrauterine life, and it is thought to play a subsidiary role after birth.

Results of studies seeking to identify an association between circulating IGF-I and IGF-II levels in relation to breast cancer risk in human remain largely negative. Results from earlier studies on IGF-I suggested a positive though inconsistent association with premenopausal breast cancer (Hankinson and Schernhammer 2003); however, more recent studies based on larger prospective datasets did not support this association (Kaaks et al. 2002; Schernhammer et al. 2005, 2006). IGF-II was found to be associated with the risk of pre- or postmenopausal breast cancer in some (Grønbaek et al. 2004) but not all human studies (Holdaway et al. 1999; Li et al. 2001; Yu et al. 2002; Allen et al. 2005). Nonetheless, it is well-established that IGF-I and IGF-II can stimulate cell proliferation and inhibit cell death in many tissue types (Pollak 2000), including both normal and malignant breast tissue (Sachdev and Yee 2001). Although evidence for a link between circulating levels of IGF-I and IGF-II in adults and subsequent cancer risk is weak, it has not been explored whether any unique features of the fetal IGF system may affect the initiation or promotion of carcinogenesis in fetal mammary tissues. The fetal IGF system

differs from the adult system in several ways. IGFs and insulin are the two factors that substantially regulate fetal growth, especially in the second and third trimesters, while growth hormone plays a minor role. Furthermore, in the second half of pregnancy, the IGF-II gene is more abundantly expressed than the IGF-I gene (Hill 1990), while IGF-I becomes predominant after birth as a result of the onset of growth hormone-stimulated IGF-I production by the liver. During late gestation, the fetal circulating level of IGF-II (150–400 ng/ml) can be three to four times higher than that of IGF-I (50–100 ng/ml) (Gluckman et al. 1983; Bennett et al. 1983; Reece et al. 1994). Therefore, IGF-II has been suggested to be primarily responsible for the regulation of fetal growth (Jones and Clemmons 1995; Allan et al. 2001).

3.3.1.3 Insulin

Insulin is known to have a significant mitogenic effect in normal mammary tissue as well as breast cancer cells (Belfiore et al. 1996; Papa and Belfiore 1996). The concentrations of insulin receptors were found to be higher in breast cancer tissues than in normal breast tissues (Papa et al. 1990), and directly related to tumor size (Papa et al. 1990), grade (Papa et al. 1990), and mortality (Mathieu et al. 1997). Epidemiologic studies have provided suggestive but conflicting results with regard to the effect of fasting insulin and the risk of breast cancer (Xue and Michels 2007b). However, more consistent results were generated suggesting that breast cancer is associated with levels of C-peptide (Xue and Michels 2007b), which is generally used as a marker to reflect insulin secretion (Clark 1999).

Because insulin receptor shares structural similarity with IGF-1 receptor, insulin can exert direct effect on fetal growth by binding to IGF-1 receptor (Grassi and Giuliano 2000). Further, insulin can also influence fetal growth by reversely controlling the expression of IGF binding proteins and thus regulating the bioavailability of IGF to high affinity receptors (Hill et al. 1998). Epidemiologic studies have suggested that the pattern of fetal growth can be influenced by maternal diet and metabolic function (Gluckman and Hanson 2004) and maternal insulin levels (Chiesa et al. 2008).

3.3.2 Hormone Alteration, Breast Stem Cells, and Carcinogenesis

3.3.2.1 Steroid Hormone and IGFs and Breast Development

Stem cells have the potential to perpetuate through self-renewal and generate mature cells of a particular tissue through differentiation (Reya et al. 2001). The differentiating potential of the human mammary gland is reflected by its development. The mammary gland is not fully developed at birth (Russo and Russo 1987) and in the human progresses through several stages, from in utero through the completion of the first full-term pregnancy. The development of the embryonic mammary gland culminates in a vesicle that contains colostrum at birth (Russo and Russo 2004). The stem cells further divide and become epithelial cells, alveolar cells, and myoepithelial cells. The mammary gland parenchyma consists of ducts terminating in end buds before puberty, undergoes proliferation and differentiation resulting in increased alveolar lobes during puberty (Rudland et al. 1996), and reaches maximal differentiation upon the first full-term pregnancy and lactation (Russo and Russo 1987).

Circulating hormone levels influence the growth of the mammary gland, with estrogen inducing ductal growth and progesterone promoting alveolar lobes (Rudland et al. 1996). Estrogen is the major steroid mitogen for the luminal epithelial cell population, which is often the target for carcinogenic transformation (Anderson et al. 1998). Estradiol has proliferative potential and affects DNA synthesis through binding to estrogen receptor in mammary epithelium. Steroid hormones modulate the synthesis of stimulatory and inhibitory growth factors, and growth factor receptors and binding proteins (Kenney and Dickson 1996).

Similarly, growth hormone, IGF-I and IGF-II also play a fundamental role in regulating the development of mammary gland by affecting proliferation, differentiation, and apoptosis of breast tissue (Laban et al. 2003). IGFs may also interact with estrogen in influencing mammary gland development by affecting the phosphorylation and function of steroid receptors and potentiating or reducing the mitogenic

effect of steroid hormones (Kenney and Dickson 1996). Furthermore, IGF-I receptor gene expression was found to be upregulated in *in vivo* models, where normal human breast epithelial cells were treated with estradiol, and in *in vitro* models, where malignant cancer cells were treated with estradiol (Clarke et al. 1997).

3.3.3.2 Breast Stem Cells and Breast Cancer

It has been speculated that stem cells represent the cellular origin of cancer, as they exist quiescently over long periods of time, and therefore could accumulate mutations that eventually lead to cancer when stimulated to proliferate (Sell 2004). A relation between stem cells in the mammary gland and carcinogenesis was suggested by Rudland and Barraclough (Rudland and Barraclough 1988). At least a portion of breast cells have a long half-life, similar to stem cells, and play an important role in breast carcinogenesis, because a subset of breast cancers recur 10 years after initial diagnosis and excision of the primary tumor (Rosen et al. 1989).

The fetal mammary gland starts to develop at about 8–15 weeks of gestation, possibly as the progeny of a single embryonic stem cell (Kordon and Smith 1998). During the prenatal period, mammary gland cells are in a partially undifferentiated state and may be more susceptible to cancer initiation (Russo and Russo 1996), particularly considering intrauterine exposure to high levels of estrogen and growth factors that favor cell replication (Gluckman et al. 1983). Trichopoulos postulated that intrauterine exposure to high levels of estrogen and IGFs may favor the generation of breast stem cells, and the number of these cells is directly related to mammary mass, which provides increased opportunity for genetic mutations (Trichopoulos et al. 2005). Ekbom et al. reported that high-density mammographic parenchymal pattern (P2 or DY) was significantly associated with the weight of placenta, which is the main estrogen-generating organ during pregnancy (Ekbom et al. 1995). The observation suggests that altered intrauterine exposure to estrogen may be associated with breast cancer risk by increasing mammary density.

3.3.3 Current Pathologic Hypotheses About Breast Carcinogenesis

3.3.3.1 Multifocal Origin

Breast cancer is a complex disease with a wide range of morphology. Based on classic whole-organ studies, it has long been postulated that most *in situ* and invasive breast cancer cases are multifocal, multicentric, or diffuse (Gallager and Martin 1969; Holland et al. 1985). In 1975, Wellings et al. proposed that most lesions referred to as mammary dysplasia or fibrocystic disease arose in terminal ductal-lobular units (TDLU) or in the lobules themselves, based on the histological examination of whole human breasts. These lesions include apocrine cysts, sclerosing adenosis, fibroadenomas, various forms of lobules (sclerotic, dilated, hypersecretory, hyperplastic, atypical, or anaplastic), ductal carcinoma *in situ*, and lobular carcinoma *in situ* (Wellings et al. 1975). This postulation was later widely accepted as the classic theory of breast cancer development: most malignant tumors of the breast originate from the epithelial cells of the lobules, which are terminal ductal-lobular units and spread to the ducts and other lobules by migration of the malignant cells.

3.3.3.2 Single-Lobe Origin

Traditional whole-organ studies using routine histological techniques often do not allow repetition of results. Recently, the traditional theory of multifocal origin of breast cancer was challenged by findings from more modern diagnostic techniques that offer more thorough analysis of the extent and distribution of lesions in a breast carcinoma. Tot and colleagues have examined and analyzed more than 5,000 consecutive breast cancer cases over 20 years using advanced methods involving two- and three-dimensional large histological sections with detailed and systematic radiopathologic correlation (Tot 2005). They found that many cases of ductal carcinoma *in situ* demonstrate continuous distribution along the ducts over several centimeters. Such a distance is unlikely if the origin of the process was a few individual terminal units, which are typically millimeters in size. In

addition, the migration of the malignant cells from the epithelial cells of the lobules to the ducts and other lobules is not supported by histological examinations. It was then postulated that ductal carcinoma in situ, and consequently breast carcinoma in general, is a lobar disease, i.e., that simultaneously or asynchronously occurring in situ (and invasive) tumor foci belong to a single lobe in one breast (Tot 2005). If this new hypothesis is proven true, it may suggest new approaches to reduce the incidence of breast carcinoma by selective visualization, excision, or destruction of the sick lobe before the malignant lesions develop (Tot 2007).

3.3.3.3 Intrauterine Risk Factors and Single-Lobe Origin of Breast Cancer

The mammary gland parenchyma develops from a single epithelial ectodermal bud. The prenatal development of the mammary gland has been suggested to include ten stages, including ridge, milk hill, mammary disk, lobule type, cone, budding, indentation, branching, canalization, and end-vesicle. At birth, the mammary gland is composed of very primitive structures: ducts ending in short ductules, lined with one or two layers of epithelial and one of myoepithelial cells (Russo and Russo 2004). The structures in the newborn mammary gland grow and branch, producing terminal end buds, which develop into alveolar buds. The buds further develop into primitive lobules of alveolar buds, which consists of three to five lobes and continue to divide until reaching the greatest number in puberty (Rudland 1993).

As intrauterine exposures to potential carcinogens have been suggested to initiate and/or promote breast cancer development before birth, carcinogenesis is expected to affect breast stem cells, which are undergoing branching into the primitive structure of mammary lobes. Though the ramification and branching process is almost complete during intrauterine life, lobularization mainly occurs during the postpubertal period (Tot et al. 2002). Indeed, there are relatively few terminal ductal-lobular units before puberty (Vogel et al. 1981). Therefore, the genetic mutations or epigenetic abnormalities involved in breast cancer development are more likely to be perpetuated by cells undergoing continuous branching and ramification while the lobe is being formed, rather than

originating within the terminal ductal-lobular units, the majority of which are not developed before birth. These postulations are in accordance with the hypothesis of the “sick lobe” by Tot and colleagues (Tot 2005, 2007).

3.4 Conclusions

Findings from epidemiologic studies suggest that markers of intrauterine exposures, such as birth weight, parental age at delivery, birth length, DES exposure, twin membership, and preeclampsia and eclampsia are associated with the risk of breast cancer later in life. Thus breast cancer may originate in utero, possibly involving the exposure of mammary stem cells to alterations of estrogen and IGFs in utero. The human mammary gland undergoes prenatal development into the primitive structure of mammary lobes, but lobularization mainly occurs during the postpubertal period. Thus it is possible that the prenatal genetic and/or epigenetic events in breast cancer development occur among cells within the same lobe through continuous branching and ramification, rather than originating within the terminal ductal-lobular units, most of which are not yet formed before birth.

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