Review

Exploring the Underlying Hormonal Mechanisms of Prenatal Risk Factors for Breast Cancer: A Review and Commentary

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Abstract

Prenatal factors have been hypothesized to influence subsequent breast cancer development. Directly evaluating the associations of *in utero* exposures with risk, however, presents several methodologic and theoretical challenges, including the long induction period between exposure and disease and the lack of certainty regarding the critical timing of exposure. Indirect evaluation of these associations has been achieved by use of proxies such as gestational and neonatal characteristics. Evidence suggests that preeclampsia is associated with a reduced breast cancer risk, whereas high birth weight and dizygotic twinning seem associated with an increased risk. Asians born in Asia have substantially lower breast cancer risks than women born in the West. Although data thus far are few, what exists is not consistent with a unifying hypothesis for a particular biological exposure (such as estrogens or androgens) during pregnancy as mediating the observed associations between pregnancy factors and breast cancer risk. This suggests that additional studies of prenatal factors should seek to broaden the range of hormones, growth, and other endocrine factors that are evaluated *in utero*. Once candidate biomarkers are identified, assessing them with respect to breast cancer and with intermediate end points in carcinogenesis should be a priority. In addition, investigations should explore the possibility that *in utero* exposures may not act directly on the breast, but may alter other physiologic pathways such as hormone metabolism that have their effect on risk later in life. (Cancer Epidemiol Biomarkers Prev 2007;16(9):1700–12)

Introduction

The study of prenatal factors may advance our understanding of breast carcinogenesis. Trichopoulos (1), hypothesized that the developing breast is influenced by the fetal environment, particularly variations in hormone concentrations, which could mediate subsequent breast cancer development. Evaluation of offspring's cancer risk with maternal and perinatal characteristics has led to several promising leads. Elucidation of the biological changes associated with these characteristics should produce a range of hypotheses on how they could affect breast cancer risk, hypotheses that could then be tested in population studies.

Discovering the underlying mechanisms responsible for prenatal risk factors may require identifying the etiologically relevant biochemical and molecular characteristics that are associated with them. Initial hypotheses focused mainly on the potential impact of *in utero* estrogen exposure, based on the high concentration of this hormone during pregnancy and its wide variation between women, as well as its role in cancer progression (1). Since then, speculation has evolved to include other hormones, other types of endocrine and growth factors, and nonhormonal changes. Data to address these in relation to pregnancy characteristics are presently accumulating. Moreover, there is emerging recognition that the associations of prenatal factors with breast cancer risk may not result from direct effects on the breast, but may instead be mediated through changes in other physiologic factors that exert their influence on breast cancer risk in adult life.

In this review, we summarize the human data on biological changes that are associated with several maternal, gestational, and perinatal characteristics that have been linked with subsequent breast cancer risk in daughters. The intent is to facilitate the interpretation of the epidemiologic literature and to refine existing biological hypotheses and generate additional ones. A comprehensive review of all *in utero* factors assessed in relation to breast cancer risk is beyond the scope of this review; therefore, we have limited the discussion to those for which the evidence indicates a strong or consistent association.

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Materials and Methods

We identified human studies on the associations of various biological factors and prenatal breast cancer risk factors by PubMed searches of papers published through 2006. This was supplemented through a review of the reference lists of identified and other relevant articles. There was extensive literature for some associations, particularly describing small, clinical studies. We chose to focus on a reasonable subset of studies that were large enough (for the most part, those with a sample size of at least 50) and of sufficient quality of design and analysis to address the issues under study. When there were few studies in a particular area, we occasionally cited papers that were not as robust. In these circumstances, we indicate our opinion of the study's limitations.

Prenatal Risk Factors for Breast Cancer

Investigating the influence of *in utero* exposures on adult cancer risk is challenging, owing in part to the long induction period and the lack of certainty regarding the critical timing of exposure. Ideally, a range of biochemical and molecular markers in the fetal environment would be measured in large populations with 40 to 50 years of follow-up to identify etiologic risk factors for the daughter's breast cancer. Instead, advances have been made by characterizing pregnancies according to factors that might be expected to be associated with significant biochemical and molecular changes and then assessing these exposure proxies for their risk impact in epidemiologic studies. The study of breast cancer risk in the daughters of preeclamptic pregnancies exemplifies this approach. Preeclampsia is a complication of pregnancy characterized by hypertension and proteinuria. The earliest investigation, based on only four exposed cases, reported an increased breast cancer risk among women born of preeclamptic pregnancies (2). Two well-designed Swedish studies (3, 4) that followed, however, found strongly reduced risks (OR, 0.24 and 0.41, respectively) with adjustment for other maternal and pregnancy factors, such as maternal age, maternal socioeconomic status, maternal parity, and birth weight. In these studies, evaluation of confounding or effect modification by the daughter's adult breast cancer risk factors was not possible. Two case-control studies, one using information from the subjects' mothers (5) and the other linking birth and cancer registry data in New York State (6), reported much smaller risk reductions but were based on only six exposed cases in the latter study. Findings reported for preeclampsia from a Swedish case-control study of birth weight and breast cancer risk (7) were also consistent with a protective effect of preeclampsia for daughter's subsequent breast cancer risk. Whereas these studies overall suggest an inverse association between preeclampsia and breast cancer risk, the lack of detail regarding preeclampsia diagnosis and the small number of subjects born of these pregnancies warrant replication of these findings.

Many studies have assessed the association of birth weight as an integrative measure of prenatal nutrition and growth and development with breast cancer risk. A recent review by Michels and Xue (8) reports that the majority of studies show a positive association with an overall increased risk of 23% (95% confidence interval 13-34%) for high compared with low birth weight. Results from a pooled analysis of individual data from several studies on birth weight and breast cancer risk are forthcoming.[4]

Several studies (4, 9-14), although not all (15-18), show an excess breast cancer risk in twins compared with singletons. Epidemiologic data also seem consistent with greater breast cancer risk in dizygotic compared with monozygotic twins or singletons (4, 9, 10, 12, 14, 17), although one study found no difference in risk by zygosity (13), whereas another (19) found evidence of a lower risk in dizygotic twins. In most studies, zygosity is unknown, with the majority being dizygotic because of its higher prevalence. The hypothesis that breast cancer risk differs by zygosity of the twin pair is based on the possibility of greater hormonal exposures from the higher prevalence of two placentae, or a larger single placenta, in dizygotic pregnancies, compared with reduced exposure in monozygotic pregnancies, two-thirds of which have one placenta. Sex of the co-twin also has been hypothesized to influence the overall exposure to the daughter *in utero* beyond the number of placentae (14). Findings from some breast cancer studies (9, 10) showing differences in risk for monozygotic (all same sex) and dizygotic (half are unlike sex) twins compared with singletons are consistent with this possibility. Other data, however, show no difference in risk of early-onset breast cancer in dizygotic twins whose co-twin was male compared with dizygotic twins whose co-twin was female (13).

Another potentially important prenatal breast cancer risk factor is the mother's cultural or physical environment during pregnancy. The most pronounced variation in breast cancer rates is observed internationally. Breast cancer incidence rates in Northern and Western Europe and North America are four to five times higher than in East and Southeast Asian countries (20). Studies of migrant populations show higher breast cancer rates in population groups that tended to have migrated to the United States farther in the past (i.e., more second- and third-generation groups; refs. 21, 22). Other studies using surrogate measures of age at migration for migrants themselves imply higher rates for those who migrated earlier in their life (23). In a study in which migration factors (i.e., age at migration, number of years lived in the United States) was measured directly in breast cancer cases and controls (24), risk was a quarter to a third higher in those Asians who were born in the West compared with emigrants who were long-term residents in the United States. The higher breast cancer rate in individuals born in the West compared with even those migrants living for many years in the West could be explained in a number of ways. In the latter study, control for recognized breast cancer risk factors (nulliparity, nulligravidy, age at first live birth, parity, breast-feeding, age at menarche, and menstrual cycle length)

[4] Isabel dos Santos Silva. Bianca De Stavola, Valerie McCormack for the Pooled Analysis on Pre-Natal Factors and Risk of Breast Cancer Project. Birth size and breast cancer risk: pooled analysis of individual participant data from 31 epidemiologic studies comprising about 25,000 breast cancer cases. Personal communication.

did not explain these differences; in fact, adjustment hardly changed the risk estimates for migration status (25, 26). These observations are consistent with environmental exposures early in life explaining variation in breast cancer rates across populations (27-29) and with mother's country of residence during pregnancy and the lifestyle factors that accompany it influencing the *in utero* environment (26). However, they could also be due to greater acculturation throughout life in children born in the host country compared with those living many years there but born elsewhere.

Although not definitive, results of these studies suggest an elevated breast cancer risk with greater birth size and among dizygotic twins. Although far less studied, there seems to be protection associated with being born of a preeclamptic pregnancy. Additionally, international comparisons of breast cancer incidence rates and results of migration studies are consistent with the possibility that the mother's country of residence during pregnancy could influence the daughter's risk, perhaps indicating the importance of differences in the *in utero* environment of various ethnic/racial populations.

Prominent Hypotheses to Explain Prenatal Risk Factors

Mechanisms that Operate *In utero*. There have been a number of attempts to develop hypotheses about mechanisms that might explain the prenatal risk factors, with perhaps the most seductive ones being unifying hypotheses that suggest one mechanism that might explain all or virtually all prenatal factors. The following outlines the consistency of evidence from studies evaluating biological changes associated with each of the prenatal risk factors.

Estrogens. Of the more widely held hypotheses, the most prominent has been that fetal estrogen exposure is directly associated with subsequent breast cancer risk. Trichopoulos (1) proposed this hypothesis more than 15 years ago based on four assumptions: ''(*a*) estrogens are important component factors in breast carcinogenesis; (*b*) factors which increase the risk of cancer when they act postnatally may also increase the risk of cancer when they act *in utero*; (*c*) estrogen concentrations are at least 10 times higher during pregnancy than during other periods of adult life; and (*d*) in pregnancy, estrogen concentrations and secretion rates vary widely between individuals, and this variability is partly accounted for by exogenous factors.''

Preeclampsia. Maternal urinary estriol excretion declines late in preeclamptic pregnancies (30-32). However, circulating maternal estrogens near delivery do not seem to be lower in preeclampsia compared with uncomplicated pregnancy (33, 34). Alterations in estrogen conjugation in preeclampsia may explain why concentrations are reduced in urine (the conjugated form), but not in maternal serum (33, 35). In addition, the limited data are not consistent with lower umbilical cord blood (from here on referred to as ''cord'') estriol, estradiol, and estrone concentrations in preeclampsia (36). Clearly, additional data are warranted on maternal and cord estrogen concentrations in preeclamptic and uncomplicated pregnancies.

Birth weight. Initially, breast cancer risk associated with high birth weight was speculated to be mediated through greater fetal estrogen exposure (37) because estriol concentrations are clearly elevated in the maternal circulation of high-birth-weight pregnancies (38-42). Interestingly, maternal estriol has been observed to be associated with birth weight in United States but not Chinese women (43). Other birth size measures, including, ponderal index (39), birth length (38, 41), and placental weight (39, 41, 43), are positively associated with maternal estriol as well. Whether birth size is associated with maternal estradiol, however, is unclear (38, 41-43). In the cord, birth weight is not associated with estradiol (38, 42, 44, 45), estrone (38, 44), or androgens (38, 45), and the association with estriol is unclear (38, 42). Overall, the data imply that birth weight is positively associated with maternal but not fetal estrogen concentrations.

Twins. There is a paucity of sufficiently large, well-designed studies on hormone levels in twin pregnancies. One study showed serum estradiol to be 58% greater between 6 and 20 weeks of gestation in mothers of twins compared with mothers of singletons (46), although these results were based on only 11 twin pregnancies. Few data address differences in biomarkers by number of placentae. Urinary estrogens may be similar in pregnancies with one or two placentae (47), but these and levels of other hormonal or endocrine factors are not well studied. There are no data on estrogen concentrations in the cord blood of twin pregnancies.

Race/Ethnicity. In pre- and postmenopausal women, lower estrogen concentrations are generally found in Chinese compared with Caucasian women (48, 49), and the ratio of the estrogen metabolites 2-hydroxyestrone to 16α-hydroxyestrone metabolites may be higher (50). Data on pregnancy estrogen concentrations, however, are not consistent with observed Asian-Caucasian differences in women who are not pregnant. Albeit limited by few studies to date, data indicate that maternal mid-pregnancy estradiol and estriol concentrations are actually higher in Chinese compared with U.S. Caucasian women (51). Whether these differences are observed in the fetal circulation is inconclusive, although data[5] from this study on cord estriol concentrations in Asians compared with Caucasians are forthcoming.

Within the West, breast cancer rates vary by racial/ethnic background, with non-Hispanic Caucasian women at higher risk than Hispanic-American and African-American women (52), and there is some indication of differences in pregnancy steroid hormone concentrations among these groups. In mid-pregnancy, maternal estriol is elevated in Asian-Americans compared with Caucasians, African-Americans, and Hispanic-American women (53), although no differences were observed for the more biologically active estrogen estradiol in a study of Asian-Americans (mainly second generation) and Caucasians (54). Results for cord hormone concentrations are consistent with higher estriol in Asian-Canadians than Caucasians (55), and no significant differences in

[5] Troisi R, Lagiou P, Trichopoulos D, Xu B, Chie L, Stanczyk F, Potischman N, Adami H-O, Hoover RN, Hsieh C-C. Cord estrogens, androgens, IGF-I and IGFBP-3 in Chinese and U.S. Caucasian neonates.

estradiol and estrone (44), although the latter data derive from a study of Asian-Americans that were likely to be highly acculturated. Hispanic-American mothers seem to have higher estriol (53), estrone (56), and possibly estradiol (54) than Caucasians, although differences in cord estradiol and estrone have not been shown (44).

Diethylstilbestrol. A natural experiment of excess estrogen exposure in pregnancy occurred with the administration of high doses of the synthetic estrogen diethylstilbestrol (DES) to women in the 1940s to 1960s in the mistaken assumption that it would prevent miscarriage. Long-term follow-ups of the *in utero* exposed are few. The National Cancer Institute's large combined cohort study of DES-exposed daughters saw no excess in breast cancer risk for the first 40 years of life but recently has reported a steadily increasing risk from age 40 to 50 years and older (57). The study investigators believe the emerging excess is real, but continued follow-up will help confirm it.

Summary. The available data are not consistent with the prevailing hypothesis that elevated *in utero* endogenous estrogen exposure is a unifying hypothesis that explains most identified prenatal risk factors for breast cancer risk in daughters. Circulating estrogen concentrations are higher in Asian pregnancies and in Asian-American neonates. In addition, maternal and cord estrogen levels are not reduced in preeclampsia, a condition associated with reduced breast cancer risk in the daughter. Whereas birth weight is positively associated with maternal estrogens, the evidence overall for cord estrogens is equivocal and indicates that birth weight is not associated with the most potent estrogen, estradiol. There is insufficient data to characterize estrogen levels in twin pregnancies with regard to the fetal circulation and by zygosity. In contrast to these physiologic risk factors, recent evidence from pharmacologic exposure to estrogen during pregnancy implies that this may be associated with an excess relative risk of breast cancer in women over age 40. Whether this is due to estrogenic activity or other carcinogenic aspects of this chemical or alterations in endogenous hormones resulting from high pharmacologic estrogen doses remains to be determined.

Androgens. It has also been suggested that exposure to elevated androgen concentrations mediates the associations of prenatal factors with breast cancer risk (33, 58). Siiteri (33) has speculated on a possible role for androgens in decreasing breast cancer risk among daughters born of preeclamptic pregnancies. Low expression of the aromatase gene, or a small or impaired placenta, as found in preeclampsia, increases the release of androgens from the placenta late in pregnancy when the fetal adrenal gland, the source of dehydroepiandrosterone (DHEA)-sulfate, undergoes rapid growth. Markedly elevated levels of these androgens result in the virilization of female fetuses (59). Less dramatic elevations, accompanied by low sex-hormone binding globulin in fetal blood, might confer long-term protection against breast carcinogenesis by antagonizing the effect of estrogens on ductal development in the fetal breast. Another possibility is that androgen exposure reduces the initial population of breast stem cells. Androgen effects on embryonic mammary gland development in males support this hypothesis (60). In the mouse model, destruction of embryologic mammary gland anlagen (initial clustering of precursor cells that eventually form mature breast tissue) by testosterone occurs during a specific period in early pregnancy, and this androgen sensitivity is expressed in female and male glands (60).

Preeclampsia. Maternal androgen concentrations by the second half of pregnancy are elevated in preeclampsia (33, 34, 61, 62), although whether levels differ earlier in pregnancy is unclear (63). Normal maternal DHEA levels (the substrate for androgen synthesis) in the presence of elevated androstenedione and testosterone (33) are consistent with *in vitro* studies showing reduced conversion of androgens to estrogens in placental tissue from preeclamptic pregnancies (64). Data on androgen levels in the cord are lacking. In one study, cord testosterone was more than 20% higher in preeclamptic pregnancies but not statistically significant (36).

Birth size. Data are limited on the association of birth size and maternal androgens. One study showed no association with DHEA, DHEA sulfate, androstenedione, and testosterone measured at the end of pregnancy (38); however, another larger study found higher maternal testosterone levels at weeks 17 and 33 in the lower-birth-weight babies (65). In the cord, birth weight was not associated with androgens in two studies (38, 45). Thus, there is little evidence that birth weight is positively correlated with maternal or cord androgens, although additional studies are necessary.

Twins. Data characterizing androgen concentrations, especially in the cord, are lacking for twin compared with singleton pregnancies. One small study showed testosterone concentrations to be 50% higher between 6 and 20 weeks of gestation in mothers of twins compared with mothers of singletons (46). Cord androgen levels in twin pregnancies have not been studied, but evidence indicating phenotypes indicative of masculinizing effects on the female (66) in unlike-sex diplacental pregnancies are hypothesized to be mediated by low levels of androgen transfer from the male to female fetus.

Race/Ethnicity. Whereas androgens have been generally lower in pre- and postmenopausal Asian compared with Caucasian women (48), a recent study showed an inverse correlation with increasing westernization in Asian migrants to the West (67). Published data on androgen concentrations in the maternal and fetal circulation, however, are unavailable, although data[5] from a study of Chinese living in Shanghai and Caucasians in Boston on cord androstenedione and testosterone concentrations are forthcoming. Umbilical cord blood DHEA sulfate is higher in Asian-Canadians than Caucasians (55). Compared with Caucasians, androgen concentrations in African-American mothers are higher (38, 56, 68, 69), whereas higher androgens have not been observed in the cord (38). Hispanic-American mothers also may have higher androstenedione than Caucasians (44).

Summary. Elevated androgen concentrations have been observed in preeclamptic pregnancies and in Asian and African-American compared with Caucasian pregnancies. These observations would be consistent with a protective effect of prenatal androgens on breast cancer risk, but the data, particularly for cord concentrations, are sparse. In contrast, there is no evidence of a positive

association of androgen concentrations with birth weight, and direct comparisons between twins and singleton pregnancies are lacking.

Other Growth and Endocrine Factors. Other growth and endocrine factors have been suggested as mediating the associations of prenatal factors with breast cancer risk, including insulin-like growth factors (IGF; ref. 70). IGFs and other growth factors have been investigated for their role in breast cancer etiology (71) and are likely related to other early-life breast cancer risk factors such as height and timing of puberty (72). Immunologic mechanisms, in particular α-fetoprotein (AFP) levels, also have been suggested as possibly mediating effects of pregnancy characteristics on maternal breast cancer risk (73) and may be important in the daughter's risk as well.

Preeclampsia. The role of IGFs in preeclampsia is unclear. IGF-I is a major growth factor and mitogenic agent, whereas in general, the IGF binding proteins (IGFBP) regulate/counterregulate its effects. Maternal (74) and cord (75) IGF-I concentrations seem lower in preeclampsia, whereas the most abundant binding protein with the highest affinity for IGF-I, IGFBP-3, is similar in preeclampsia and uncomplicated pregnancy in maternal (76) and cord samples (75, 76) in the absence of intrauterine growth retardation. IGFBP-1 levels may be lower in preeclampsia early in pregnancy (74), but similar in the maternal circulation at delivery (76) and in the cord (75, 76). These results suggest that the IGF profiles in preeclampsia are complex and dynamic throughout pregnancy, but are consistent with the possibility of lower IGF-I mediating the reduced breast cancer risk associated with this condition.

Other hormones involved in glucose metabolism and energy balance also seem altered in preeclampsia. Gestational diabetes (77) is more common in preeclamptic pregnancies, as are low levels of sex hormone-binding globulin (SHBG), a marker of insulin resistance and hyperinsulinemia (63). Maternal (34, 78) and cord (79) leptin concentrations may be elevated in preeclampsia. Adiponectin, a hormone associated with increased insulin sensitivity, is elevated in the maternal circulation late in preeclamptic compared with normal pregnancies (78); however, levels early in pregnancy may be reduced (80). The association of preeclampsia with maternal third-trimester levels of resistin, a hormone possibly involved in insulin resistance and inflammation, is equivocal (78, 81).

Other hormones, proteins, and tumor markers that have been investigated in relation to breast cancer have also been studied for their role in preeclampsia. Maternal progesterone concentrations may be elevated in preeclampsia (82). Human chorionic gonadotropin (hCG) is elevated in preeclamptic compared with normal pregnancies (64, 83), and most studies show higher AFP concentrations in the fetal (84) and maternal circulation (85, 86), with a stronger association for severe disease (84, 86). Inhibin A, a hormone that inhibits the production of follicle-stimulating hormone, was increased in the circulation of preeclamptic mothers in two (83, 87) of three studies (86).

Birth size. Birth size seems to be positively associated with maternal progesterone (41, 43). Low maternal pituitary growth hormone, a possible marker for increasing placental growth hormone concentrations (88), is associated with greater birth size (43). Most studies addressing the associations of the IGF system with birth size have focused on differences between small for gestational age neonates resulting from a variety of etiologies and appropriate for gestational age neonates; however, the greatest breast cancer risks are observed for women born heavy. In studies conducted in normal pregnancies with a range of birth weights, the positive association between birth size and cord IGF-I concentrations is well established (89-98). IGFBP-3 has also been positively associated with birth size in most studies (75, 95, 96, 99), whereas IGFBP-1 may be inversely associated (90, 95). Associations of IGF-2 with birth size are unclear (92, 93, 99), as is the role of IGFBP-2, the main IGFBP in the fetal circulation (99). In contrast, birth weight is generally not associated with concentrations of IGF-I (100, 101), IGFBP-1 (100-102), or IGFBP-3 in the maternal circulation (103). Thus, birth weight and other measures of birth size are positively associated with cord, but not maternal levels of IGF-I and IGFBP-3, and inversely associated with cord IGFBP-1.

The roles of other hormones involved in energy homeostasis and growth hormone stimulation have been investigated. Leptin concentrations are positively associated with birth weight and several other measures of birth size in the cord (79, 94, 97, 104-111), but not in the maternal circulation (110), and studies show a lack of correlation between the two sources (105, 107, 112). Results of studies addressing the association of adiponectin levels with birth weight are unclear for both cord (113-116) and maternal levels (114, 117). Likewise, the associations of cord or newborn concentrations of ghrelin with birth size are inconsistent with some indication of an inverse (97, 118, 119) or null association (120, 121).

Several growth factors, including steroid hormones, IGF-I, IGFBP-3, and leptin, are indicated in prenatal growth; however, the associations are not consistently observed in the cord and maternal circulation. In general, maternal but not cord levels of several steroid hormones (estrogens and progesterone) are positively associated with birth size, whereas positive associations with cord but not maternal concentrations of IGF-I, IGFBP-3, and leptin are observed.

Twins. There is an even greater lack of data on hormones other than estrogens and androgens and other biomarkers in the fetal circulation of twins compared with singletons. Higher levels of α-fetoprotein (122), human placental lactogen (123, 124), and progesterone have been observed in mothers pregnant with twins compared with those pregnant with singletons (123). Maternal (122, 125) and cord hCG may be higher in twins compared with singletons (125), but may be similar in like and unlike sex twin pairs (125). Compared with singletons, leptin levels measured a day after birth were lower in a study of dichorionic twins (126), but were elevated in amniotic fluid of twins (127). Interleukin-1β, interleukin-4, and tumor necrosis factor-α may be elevated, and leukemia inhibitory factor and migration inhibitory factor-related protein 8 and 14 may be reduced in the amniotic fluid of twins compared with singletons (127). No differences in maternal IGF-I or IGFBP-3 concentrations were shown in two small studies comparing twin and singleton pregnancies (124, 128).

Race/Ethnicity. Maternal mid-pregnancy prolactin, progesterone, human growth hormone, albumin, SHBG, and possibly α-fetoprotein concentrations may be higher in Chinese compared with American women (129). Whether these differences are observed in the fetal circulation is unknown.

Additional hormones, growth factors, and other biological features of pregnancy have been investigated for racial/ethnic differences among pregnancies occurring in the West. Maternal hCG levels (53, 130) are generally higher in Asian-Americans, and α-fetoprotein levels are generally higher in Asian-American (53, 131) and African-American women (53, 69) than in Caucasians. IGF-I may be higher in African-American and Hispanic-American mothers compared with Caucasians (54), and IGFBP-3, a major determinant of bioavailable IGF-I, may be reduced in Asian-American and Hispanic-American compared with Caucasian pregnancies (44). No differences by race/ethnicity have been shown for IGF-I, IGF-2, and IGFBP-1 (44). Other hormones involved in glucose metabolism and energy balance such as leptin and ghrelin seem similar in the cords of Asian-American and Asian-Canadian and Caucasian neonates (55, 130).

Summary. The role of other growth and endocrine factors in explaining the associations of *in utero* exposures with breast cancer risk are unclear. IGF-I is clearly elevated in larger babies and may be reduced in preeclampsia, but whether it differs by race/ethnicity is equivocal. Leptin is also elevated in larger babies, but in preeclampsia as well, which is inconsistent with a protective effect on breast cancer risk. α-Fetoprotein is elevated in pregnancies with characteristics associated with a reduced breast cancer risk such as Chinese and African-American race/ethnicity and preeclampsia and may be inversely related to birth weight. However, in twins who are at increased breast cancer risk, AFP seems elevated.

Angiogenic Factors. Markers of the balance of pro- and antiangiogenic factors in adults have been linked to breast cancer risk and prognosis. Placental growth factor (PlGF) and other members of the vascular endothelial growth factor (VEGF) family of angiogenic factors are necessary for tumor angiogenesis, and recent work suggests that PlGF is predictive of breast cancer recurrence, metastasis, and patient mortality (132). In addition, the ratio of soluble VEGF receptor (sFlt-1) to VEGF differs significantly between breast cancer cases and controls and is associated with tumor size (133). Endostatin, another antiangiogenic protein, has been shown to be inversely correlated with angiogenesis in breast cancer patients (134). *In utero*, VEGF is an important factor in the mobilization and differentiation of epithelial progenitor cells in the fetal circulation (135).

Preeclampsia. The etiology of preeclampsia is likely to involve immunologic, inflammatory, and angiogenic abnormalities, and there is a large literature on biological and molecular markers of these processes aimed at early disease prediction and treatment (136-139). Especially promising are results of research focused on the balance of major angiogenic and antiangiogenic proteins (140). In preeclampsia, high levels of the antiangiogenic protein *sFlt-1* seem to bind with and neutralize the proangiogenic effects of free PlGF and VEGF, resulting in low levels of their bioactive forms. Other antiangiogenic factors, for example, endostatin, also seem elevated in maternal blood of preeclamptic compared with normotensive pregnancies (141). Data show higher concentrations of the antiangiogenic protein soluble (s-) endoglin in preeclampsia as well, and in one study, preeclampsia risk was elevated most among women in the highest levels for both s-endoglin and the ratio of sFlt1 to PlGF (142). Recently, reduced cord blood VEGF (143, 144) and PlGF (144) and elevated sFlt-1 concentrations were shown in preeclamptic compared with uncomplicated pregnancies (144).

Twins. Angiogenin, a proangiogenic factor, may be elevated in amniotic fluid of twins compared with singletons (127).

Summary. Angiogenic balance has emerged as a key determinant of preeclampsia and provides a novel biological mechanism for the reduced breast cancer risk observed in daughters of these pregnancies. The possibility of higher proangiogenic factors in twins is consistent with relatively angiogenic states *in utero* being adverse for subsequent breast cancer risk. Characterizing angiogenic profiles in association with other *in utero* factors associated with breast cancer risk might prove to be informative.

Methodologic Issues. Many of the inconsistencies in the literature and lack of definitive support of the more prominent hypotheses lie in methodologic limitations in much of what research has been conducted. Several of these issues have impeded our attempts to understand the biology of pregnancy conditions with direct implications for the daughter's *in utero* exposure. Previous clinical studies have generally been limited by small sample sizes, lack of information on covariates, and inappropriate control groups. Moreover, only recently have advances in steroid hormone assay methodology allowed reasonably valid measurements for use in research studies (145). Most studies have measured hormones and other biomarkers in the maternal circulation due to the difficulty in directly sampling the *in utero* environment and based on the assumption that maternal hormones and other endocrine factors reflect those in the fetal circulation because of the highly integrated maternal-placental-fetal unit. However, the degree of correlation between, for example, estrogen and androgen concentrations in the maternal and fetal circulations, seems modest (146); thus, findings based on maternal sampling may be appropriate for understanding the mother's hormonal exposure but not immediately relevant to the daughter's. For each candidate biomarker, the concordance between maternal and fetal values should be assessed.

Inferences drawn from findings based on both maternal and cord measures are limited by the degree to which they reflect the time period of mechanisms that influence breast carcinogenesis. Direct exposures to the breast during a critical developmental window may be important but difficult to ascertain (147). Associations of biomarkers with gestational characteristics may change over the course of the pregnancy, however, and without less invasive methods for sampling the fetal circulation, assessing maternal levels may be necessary. Furthermore, sampling at delivery may not represent late-pregnancy levels if only by virtue of stress from the labor and delivery. In some cases, the prenatal factor, for example, preeclampsia, may be related to whether blood

is collected before or after labor starts because induction is more likely in these pregnancies.

Mechanisms Operating through Changes in Adolescents and Adults. The above hypotheses dealt with mechanisms proposed to operate *in utero*. Other hypotheses suggest that prenatal risk factors operate through mechanisms that involve changes to hormone metabolism or other metabolic processes that are affected *in utero*, possibly through epigenetic mechanisms, but are expressed later in life, perhaps during adolescence, pregnancy, or lactation. Alternatively, pregnancy characteristics may be markers for risk factors for conditions that are themselves the true biological factors associated with later cancer risk.

Preeclampsia. Daughters of preeclamptic pregnancies may have higher blood pressure in adolescence (148, 149), but may be similar to daughters of normal pregnancies in age at menarche (148, 150, 151), and levels of fasting insulin and glucose, cortisol, and DHEA sulfate (149). Whether adolescent and early adult weight and body mass index differ is unclear (148, 151).

Birth size. High birth weight may be positively associated with childhood (152) and adolescent height (153). However, estrogen and androgen concentrations seem elevated in prepubescent children who had lower birth weights, independent of current weight (154, 155), and data consistently indicate that menarche is earlier in these girls (152, 153, 156-158). In fact, epidemiologic data seem to indicate that the association of high birth weight with breast cancer risk in premenopausal women is not likely to be mediated through height, weight, or growth velocity in childhood and adolescence (159, 160), but possibly through greater adult height (161). Whether birth size is associated with premenopausal estrogen concentrations (162, 163) or adult IGF profiles (164-167) is unclear.

Twins. In a study of testosterone levels in 13-year-olds, there was no difference between same-sex and unlike-sex female twins (168).

Summary. Few associations of prenatal breast cancer risk factors with adolescent and adult breast cancer risk factors have been explored. There is some evidence of links, but even in these circumstances, the data are so few as to be inconclusive.

Prenatal Risk Factors for Maternal Breast Cancer. There have been suggestions that some of the postulated prenatal risk factors may be risk factors for breast cancer development in the mother as well. This should be much more easily assessed than for the offspring because the latency between the pregnancy event and the development of cancer is much shorter, and the study subject can provide a more reliable history of the risk factor. Despite this, it is unclear whether these prenatal risk factors are also maternal risk factors.

The evidence of an effect on maternal risk is perhaps best for preeclampsia where breast cancer risk is lower in women who experienced preeclampsia or hypertension during pregnancy in most (64, 169-172), but not all studies (173, 174). Moreover, data from the Child Health and Development Studies show a marked reduction in breast cancer risk with elevated mean arterial pressure (175), and systolic blood pressure increases from mid- to late pregnancy below the diagnostic criterion for hypertension (58). Breast cancer risk also was independently associated with other markers of placental compromise, including maternal floor infarction and smaller placental size. Taken together, these data suggest that the observed protection for breast cancer could be related to chronic cardiovascular factors as well as to placental abnormalities that are seen in preeclampsia.

The association of birth weight and maternal breast cancer risk has been assessed in several studies (58, 173, 176-178), with only one showing a small risk elevation (179), although two studies (58, 173) reported positive associations with placental size. Similarly, most studies show no association of multiple births with maternal breast cancer risk (169, 171, 176, 180-185). Three studies actually found a reduced risk in mothers of multiple births compared with singleton pregnancies (186-188), whereas only one found an elevated risk (189).

The emerging evidence for preeclampsia and associated conditions being related to maternal breast cancer risk could be a major benefit to the identification of the underlying biological rationale for its role as a prenatal risk factor under at least two different scenarios. If the underlying cause is the same for the mother's and the offspring's reduced risk, then identifying the relevant biomarker of this mechanism should be much easier in the mothers, given the much shorter time between the measurement of the biomarker and the development of cancer and due to the obvious relevance of assessments of the maternal circulation and the comparative ease of doing this versus the fetal circulation. A second possibility is that some inherited factor is responsible for the reduced breast cancer risk, and that this same factor is either the cause or highly correlated with the cause of the preeclampsia. This seems less likely because it would imply that in the case of correlated causes, either preeclampsia or breast cancer in the presence of preeclampsia would need to be a highly familial trait, at a level much stronger than that for breast cancer or preeclampsia in general, currently estimated at about 2-fold for first-degree relatives. However, if this is the underlying rationale, then the recent marked advances in our understanding of underlying mechanisms for, and biomarkers of, preeclampsia (see the above discussion of angiogenic factors) could provide exceptional opportunities to identify the mechanism for any such familial risk.

Future Directions

Future research can be thought of in three components: the identification of prenatal risk factors for breast cancer, the characterization of the biochemical and molecular events associated with or resulting from these risk factors, and the relationship of these events to subsequent breast cancer risk. Very few potential prenatal risk factors have been investigated, and the information on those that have is remarkably limited. Even for the risk factors focused on in this review, the amount and strength of the evidence are less than desirable. The marked protective effect of preeclampsia is based essentially on one record-linkage study (4). Although birth weight is becoming an accepted risk factor for breast cancer, the excess risks are relatively

small, and the overall effect is still being pursued in various pooling efforts. As for twinning as a risk factor, the inconsistencies in findings and important gaps in data are major as we have summarized. Certainly, one future direction should be to replicate and fill in the gaps for risk factors already considered, as well as explorations of the effects on breast cancer risk of the myriad of other prenatal characteristics and exposures that might be relevant.

The characterization of biochemical and molecular events associated with, or resulting from, established prenatal risk factors is the main focus of this review. As described, there remains a considerable lack of such data directly relevant to help us understand the biology linking these maternal, fetal, and gestational factors with breast cancer risk. Future studies in this area should not be focused on one underlying biological hypothesis because there are clearly a number of potentially biologically relevant changes that can occur with these risk factors, and with the investment required to conduct these studies, assessment of as many of these potentially causal pathways as possible would be prudent.

Finally, investigation of the promising biological pathways emerging from these efforts, for their relationship to subsequent breast cancer risk, will be the most challenging task. Indeed, with the time lag involved between these events and the occurrence of breast cancer, most investigators have suggested evaluating these pathways and their biomarkers in relation to potential intermediate end points in breast carcinogenesis. Thus far, the potential end points most prominently mentioned include markers of breast ductal-cell mass, breast stem cell populations, specific molecular changes in breast tissue (e.g., genetic and epigenetic), and alterations in adult hormonal profiles. The current lack of validated and feasible markers for these end points is a major limitation to investigating their links to prenatal factors and biological pathways. Indeed, this is also a severe impediment to the ability to link these potential intermediate end points with breast cancer risk, a key requirement for them to be considered true intermediate end points.

Historically, speculation about *in utero* factors has centered on their effect on the amount of mammary gland mass, which has been thought to correlate positively with disease probability (190). Indirect measures of mammary gland mass such as breast size have been positively associated with breast cancer risk in lean women where it may be less likely to reflect adiposity (191, 192). High-density parenchymal patterns have also been considered a surrogate for mammary gland mass and are strongly associated with breast cancer risk (193, 194). Interestingly, data show that among Chinese women who migrated to the United States, the most acculturated have the densest breasts, and that this is not explained by reproductive and lifestyle factors related to density (195). Whereas high-density patterns are a surrogate for the combination of the proportion of the breast occupied by epithelium and stroma (192), their correlation with actual ductal mass is unknown. Finally, the causal relevance of ductal mass is still simply a hypothesis. If ductal mass is the relevant factor with regard to breast cancer risk, a reliable marker will need to be validated. Progress might be made in autopsy studies in which mammography data and assayed amount of ductal mass could be correlated.

Recent speculation has focused more specifically on the number of breast stem cells (196), the cells most likely to become malignant *in vitro* and in animal models (197). Progress has been made in identifying mammary-specific stem cells (197), but the relationship of the adult mammary cell population with embryonic stem cells is not established (198). Nevertheless, these developments have increased enthusiasm for addressing whether early-life breast cancer risk factors are related to stem cell prevalence. In one study, the associations of stem cells in cord blood, as a surrogate for breast stem cell number, are being investigated with regard to steroid and growth hormones (199). Recent data implicate reduced levels of epithelial progenitor cells in the cord blood of pre-eclamptic pregnancies, which may be a marker of stem cell reduction (143). Whether cord blood stem cells or epithelial progenitor cells are correlated with breast-specific stem cells, however, is unknown. Thus, there are several avenues of research that would be required to provide evidence to evaluate the assumptions on which these hypotheses relating *in utero* events to breast carcinogenesis are based.

Another issue is the lack of data on the developmental aspects of the breast in relationship to any of the suggested etiologic factors. Many of the hypotheses that have been proffered make assumptions, frequently speculative, about the roles of hormones or other factors in the embryology of the breast. For example, the relationships between *in utero* exposures such as estrogens or other growth factors and mammary gland mass, mammographic densities, and other intermediate markers, and the underlying biology have not been described. Research on effects of *in utero* exposure to the synthetic estrogen DES in animal models could provide some insight. There is sufficient evidence of teratogenic and carcinogenic effects of DES on the reproductive tract tissue, but similar studies on other organ systems, including the breast, are not currently available (200). Knowing the biological effects of compounds such as DES in human breast development could provide some credibility to the hypotheses raised. Detailed information on mammary gland embryogenesis does indicate to date that fetal gland development seems to be independent of steroid hormones until the 15th week of gestation when testosterone affects the breast structure, and that in late gestation, the fetal breast is responsive to steroid hormones and prolactin (201). This, along with emerging information on embryologic breast development, should be incorporated into the interpretation of epidemiologic data.

A more feasible issue to address is changes to later hormone metabolism associated with prenatal events. Cohort studies with the ability to either follow or identify offspring of pregnancies characterized by conditions associated with breast cancer risk present this opportunity. When there is the ability to link with cancer incidence, the effort should be made to directly test whether the biomarker explains any of the association of the pregnancy exposure and risk. For example, the subsequent hormonal and other endocrine status of women born of preeclamptic pregnancies may elucidate mechanisms involved in the reduced breast cancer risk they experience.

The focus of research should ideally shift from speculation toward more direct tests of these hypotheses.

It may be difficult to accomplish this by directly studying associations of prenatal exposures and breast cancer risk. Thus, agreement on reasonably definitive ways of ruling in or out a hypothesis in the absence of such direct data is needed.

Conclusion

Identification of *in utero* and early-life risk factors for breast cancer has spawned a number of speculations about underlying biological mechanisms. The limited attempts thus far to characterize relevant biological correlates of these *in utero* risk factors have discovered a wide range that could be linked to plausible mechanisms of breast carcinogenesis. It is premature at this point in our understanding of the biology of pregnancy characteristics related to subsequent breast cancer risk to focus exclusively on one or two of these candidate mechanisms. Instead, we should seek to uncover the plausible range of hypotheses, based on a comprehensive characterization of the biochemical and molecular consequences of these risk factors. We can then proceed to compare the relative credibility of these alternative pathways by relating them to breast cancer risk. Ideally, this would be done directly, but with the practical difficulties involved in linking biological markers in early life to subsequent breast cancer risk, an alternative is to investigate these biomarkers in relation to potential intermediate markers on the pathway to breast cancer.

This process will involve major scientific and practical challenges. However, driven as it is by prenatal risk factors identified in human population studies, the results have the clear potential to give us critical insights into the basic biological pathways underpinning breast cancer development, beginning from the very earliest days of life.

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