Perinatal Sex Hormones and Risk of Breast and Prostate Cancers in Adulthood

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INTRODUCTION

Fetal origins of adult disease, such as cardiovascular diseases and diabetes, have been suggested by ecologic and individual-level studies (1). Fetal and placental growth is influenced by maternal nutrition, function of the placenta, and the hormonal, metabolic, or circulatory environment of the maternal-placental-fetal unit (2). Various biologic mechanisms—for example, effects on cell numbers, alteration of gene expression, selective survival or “natural selection” of particular clones of cells, effects on structure and function of organs, and up- or down-regulation of hormone receptors—have been proposed to explain the putative long-term effects of perinatal conditions on selected organs (2). The link between perinatal variables and the risk of adult chronic diseases, if it existed, would have profound public health implications (1).

In the area of cancer research, there has been increasing interest among epidemiologists as well as experimental scientists in the potential effects of the intrauterine environment on the risk of breast and prostate cancers. Mammary and prostate glands undergo the early phases of organ development, growth, and cell differentiation during the fetal period (3, 4), when the process of carcinogenesis in these organs may first begin (5). Many of the epidemiologists who have reported the associations between pre- and perinatal characteristics and subsequent risk of breast and prostate cancers have hypothesized that exposure to high concentrations of sex hormones during the fetal period might explain the associations (6–10). Both the breast and prostate depend on sex hormones for their growth and physiologic functioning. Thus, sex hormones may be a reasonable candidate for a mediating factor in the reported associations. However, it would be a formidable task to unequivocally demonstrate in humans that pre- and perinatal conditions influence the risk of developing breast or prostate cancer several decades later, let alone the biologic mechanisms of such effects. Major difficulty arises from the long putative induction period spanning several decades between exposure and outcome (1). Furthermore, perinatal attributes could simply be predictors of socioeconomic status (11, 12) or behavioral and biologic factors in later stages in life that might have more direct influence on cancer risk, thus resulting in confounding by risk factors during childhood, puberty, and adulthood (1). In fact, Joseph and Kramer concluded in their recent review that the observed associations were more likely biased results than evidence of a causal relation (1).

Our aim in this review is to provide an overview of findings from experimental and epidemiologic studies to evaluate whether there is enough evidence of a role of perinatal sex hormones in the etiology of breast and prostate cancers (figure 1) to warrant further investigation. For each of these two cancers, we first discuss hypothesized mechanisms and observations regarding the effects of perinatal sex hormone exposure on early organ development and long-term consequences (figure 1, A). This line of evidence would support the potential importance of perinatal conditions in carcinogenesis, although it would not demonstrate a direct link between developmental events and cancer occurrence. Next, we describe data from animal studies on the effects of pernatal sex hormone exposure on cancer development (figure 1, B). Given the extreme difficulty of testing the hypothesis directly in humans, experiments in animals may be the only way of demonstrating causal associations. Then, we summarize epidemiologic data on selected pregnancy and birth characteristics to address the following two questions: 1) Are the birth and pregnancy characteristics examined in epidemiologic studies of cancer correlated with high or low perinatal sex hormone exposure (figure 1, C)? and 2) Do epidemiologic studies show consistent results regarding the associations of the pregnancy and birth characteristics with cancer risk (figure 1, D)? Correlation between prenatal characteristics and sex hormone levels would add to the plausibility of the interpretation that the relation of those prenatal variables to cancer risk may be explained by variations in sex hormone levels. Finally, we discuss limitations of the data currently available and suggestions for future research.

BREAST CANCER

Hypothesized biologic mechanisms (figure 1, A)

The sex hormone hypothesis of the prenatal origin of breast cancer depends on the assumption that concentrations and secretion rates of endogenous estrogens during the pre-
A. Hypothesized biological mechanisms

B. Experimental data in animals

C. Correlation of pregnancy and birth characteristics with prenatal hormone levels

D. Epidemiologic data in humans

FIGURE 1. Diagram of a hypothesized causal pathway linking prenatal exposure to sex hormones and cancer risk in adulthood. Bold type indicates the categories of data and hypotheses discussed in this review.

The prenatal period affects the structure and physiology of the mammary gland, which in turn may influence the risk of breast cancer. In humans, the mammary gland goes through successive stages of development during the pre- and perinatal periods; these stages include branching and canalization that occur at about 15–32 weeks of gestation (3). Trichopoulos used the phrase "fertile soil for subsequent cancer initiation" to refer to biologic changes in the breast epithelium induced by elevated concentrations of estrogens during the fetal period (5). This concept needs to be translated into testable hypotheses involving specific, well-defined measurements of morphologic or functional variables. Such measurements would be extremely difficult in humans. However, data from animal experiments are available to support possible biologic mechanisms by which prenatal estrogen levels influence the structure and function of the mammary glands, as suggested by Anbazhagan and Gusterson (13).

First, variations in perinatal estrogen levels may induce variations in mammary gland development. Several studies in rodents have shown that prenatal exposure to high levels of sex hormones or their agonists affects the morphology of the mammary gland. For example, injection of pregnant mice with estradiol and genistein (a type of phytoestrogen, i.e., an estrogenic compound of plant origin) increased the density of terminal end buds in the mammary glands of the female offspring (14). Another study showed that neonatal exposure to estradiol or testosterone resulted in an increased number of ductal branchings in mammary glands in mice aged 33 days (15). If cancer risk were proportional to the number of stem cells as well as the rate of cell division (16), women with a larger number of breast epithelial stem cells that are targets for carcinogens would be at an increased risk of breast cancer (17).

Other hypothesized effects on mammary gland development of intrauterine exposure to higher levels of estrogens include an increased chance of in utero mutations in genes relevant to oncogenesis and an altered response of breast epithelial cells to hormones and carcinogenic agents in adulthood (13). These effects would be more difficult to measure than morphologic characteristics of the mammary glands. However, one study suggested that estrogen exposure before birth might affect the timing of sexual matura-
spring showed an earlier age at puberty (18). This effect on age at onset of puberty is relevant to breast cancer risk, because early age at menarche is an established risk factor for breast cancer in humans (19).

**Experimental data (figure 1, B)**

Animal experiments have two major advantages over epidemiologic research: 1) the exposure can be manipulated and controlled, and 2) the outcome can be observed within a relatively short time period. Thus, experimental data provide more direct evidence of a specific exposure-outcome association than human data do, although extrapolation of findings from animals to humans requires caution.

Hilakivi-Clarke et al. showed that the offspring of rats treated daily with 20 ng of estradiol during pregnancy developed mammary tumors more frequently and at an earlier age than control animals did (20). Exposure of pregnant rats to genistein also enhanced the effect of a chemical carcinogen on the incidence of mammary tumors in the female offspring (21). Similar effects were observed in the offspring of rats fed a high-fat diet during pregnancy, followed by exposure to a chemical carcinogen (20). Walker also observed an increased incidence of mammary tumors among mice whose mothers were fed a high-fat diet during pregnancy (22).

These effects of dietary fat intake during pregnancy on mammary tumors in the female offspring may operate, at least in part, through changes in estrogen levels. Hilakivi-Clarke et al. observed that circulating estradiol levels were higher in pregnant female rats fed a high-fat diet than in their counterparts fed an isocaloric diet with a lower fat content (20). Two other studies of nonpregnant female rats also showed elevated serum estrogen levels associated with high dietary fat intake (23, 24). The link between dietary fat and serum estradiol levels may be explained by various possible pathways: for example, activation of p450 aromatase, which catalyzes the conversion of androstenedione to estrone; linoleic acid metabolites; and reduced binding of estrogens to sex hormone-binding globulin (SHBG) or albumin by polyunsaturated fatty acids, thereby increasing the circulating levels of biologically potent estrogens (25). A high-fat diet may also influence the levels of estrogen receptor and protein kinase C in mammary glands of the offspring (25).

**Epidemiologic data (figure 1, C and D)**

One practical way of establishing the association between prenatal sex hormone levels and breast cancer risk in humans would be to implement a two-step approach: 1) establish the relation of sex hormone levels to characteristics of pregnancy and birth (figure 1, C) and 2) establish the relation of those pregnancy and birth characteristics to breast cancer risk (figure 1, D). That a given prenatal variable is correlated with both sex hormone concentrations and breast cancer risk would not by itself prove a causal relation between prenatal sex hormone levels and breast cancer risk. However, lack of consistent data for either or both of the two links would make the sex hormone hypothesis for the prenatal origin of breast cancer less tenable. The following sections review epidemiologic data on selected pregnancy and birth characteristics in relation to sex hormone levels and breast cancer risk.

**Parental age at birth.** Many epidemiologic studies have examined the relation between maternal age and breast cancer risk of the daughter. Case-control studies conducted between the 1960s and the early 1980s suggested an increased risk of breast cancer associated with older age of the mother (26–29), but the results from two of these studies (26, 27) did not take into account reproductive factors now accepted as established risk factors for breast cancer. Two more recent case-control studies reported an increased risk of breast cancer associated with increasing maternal age (30, 31); however, one study did not adjust for risk factors other than age (30), and, in the other study, the association was limited to parous daughters (31). Most other studies reported no association (7, 32–35), with the exception of two (36, 37) that showed borderline statistical significance for elevated breast cancer risk with increasing maternal age.

Some evidence suggests that estrogen concentrations during pregnancy are related to maternal age. In a study of maternal blood at weeks 26 and 31 of pregnancy, for instance, Panagiotopoulou et al. (38) showed that both total estrogen and estradiol levels were lowest in the youngest group of mothers (<20 years of age), highest in women aged 20–24 years, and intermediate in the older age groups (≥25 years). This pattern was observed among both women in their first pregnancy and those in their second pregnancy.

In short, parental age does not show a consistent association with breast cancer risk. Most recent studies that accounted for established risk factors for breast cancer showed no association. Furthermore, the inverse U-shaped relation of maternal age to estrogen levels observed in one study (38), with a peak concentration at age 20–24 years, does not explain the higher breast cancer risk with increasing age of the mother if high estrogen concentrations contributed to an elevated breast cancer risk.

**Birth weight.** Some studies have examined whether birth weight is associated with estrogen levels. In a study of 141 Greek women, Petridou et al. (39) found that serum total estrogen levels at week 26 of pregnancy were positively correlated with birth weight of the offspring. The regression coefficient after adjustment for age, years of schooling, occupation, parity, height, prepregnancy weight, and maternal smoking was 1.2 g (birth weight) per 1 ng/ml (estrogen concentration) (90 percent confidence interval [CI]: 0.2, 2.2). In contrast, Simmons et al. (40) reported no association between umbilical cord blood estradiol level and the birth weight of female babies. In this study of cord blood samples from female babies, birth weight was not associated with SHBG levels or with dehydroepiandrosterone sulphate levels (40). Thus, the limited available evidence is inconsistent concerning the association of birth weight with estrogen levels.

In a nested case-control study, Ekblom et al. (7) observed a J-shaped association between birth weight and breast cancer risk, with the risk being the lowest for women whose infants' birth weight was 2,500–3,000 g. However, this finding was not replicated in a larger nested case-control study by the same investigators (37). Sanderson et al. (33) found a similar J-shaped association for women younger than aged
45 years but not for older women. In a case-control study nested in the Nurses’ Health Study, Michels et al. (8) showed that low birth weight was associated with a reduction in breast cancer risk (odds ratio (OR) for birth weight <2,500 g vs. ≥4,000 g = 0.55, 95 percent CI: 0.33, 0.93). In summary, some studies suggest the association between birth weight and breast cancer risk, but the results from various studies are not consistent.

Birth rank. Maternal estradiol levels were found to be higher in the first pregnancy than in the second pregnancy in the two studies that have examined this issue (38, 41). In a study by Bernstein et al. (41), sera collected between weeks 7 and 17 of the first pregnancy was found to have higher percentages of free estradiol, a higher concentration of free estradiol, and higher concentrations of total estradiol than in second-pregnancy sera collected from the same women by 9, 17, and 7 percent, respectively, after adjustment for week of pregnancy. In an analysis stratified by maternal age, Panagiotopoulou et al. (38) showed that, at weeks 26 and 31, the difference in the estradiol levels of women in their first and second pregnancies was about 14 percent. Estradiol levels in the cord blood from female babies were also higher in firstborn than in later births (7.53 vs. 6.29 ng/ml); the difference was significant after accounting for length of labor, maternal age, and infant’s birth weight (42). No difference in cord blood testosterone levels was found between firstborn and later-born female babies (0.212 vs. 0.213 ng/ml) (42).

Hsieh et al. found that a birth rank of 2 or higher was associated with a reduced risk of breast cancer among premenopausal women (OR = 0.76, 95 percent CI: 0.60, 0.96) but not among postmenopausal women (OR = 1.03, 95 percent CI: 0.86, 1.23) (6). Three other case-control studies found no association between birth rank and breast cancer risk (26, 32, 33).

In summary, results from three studies (38, 41, 42) are consistent: higher estrogen levels occur in the first pregnancy than in later pregnancies. However, evidence supporting birth rank as a risk factor for breast cancer is limited.

Twins. Another pregnancy characteristic possibly related to both prenatal estrogen levels and breast cancer risk is twinship. Epidemiologic studies of twin membership and breast cancer are summarized in table 1.

Two epidemiologic studies, a cohort study that included postmenopausal women only (9) and a case-control study of young women (<55 years of age) (35), showed increases in breast cancer risk of 62 and 72 percent, respectively, among twin women when compared with singletons. A finding of Kappel et al. (43) regarding higher estrogen levels in uncomplicated twin pregnancies than in singleton pregnancies supports a hypothesis that prenatal estrogens contribute to the association between twinship and breast cancer risk. However, three other epidemiologic studies (26, 33, 37) did not corroborate this association.

Risk of breast cancer may be higher for dizygotic twins than for monozygotic twins (9, 37, 44). Data from the Swedish Twin Registry showed that the observed-to-expected ratio of breast cancer incidence, when all age groups were combined, was not elevated for monozygotic twins but was marginally elevated for dizygotic twins in comparison with singletons (44). A substantially elevated incidence of breast cancer in dizygotic twin women aged 20–29 years (observed-to-expected ratio = 6.7, 95 percent CI: 2.9, 13.1) found in this study may be due to chance, as no trends were observed for other age groups. The difference in breast cancer risk between monozygotic and dizygotic twins, if true, would have to be explained by factors other than estrogen levels, because estrogen concentrations do not seem to differ between the two groups (43).

The sex of siblings in multiple births may also influence sex hormone exposure. In rodents, fetuses positioned in utero between female fetuses have higher serum levels of estradiol and lower serum levels of testosterone than siblings of the same sex placed between two male fetuses (45, 46). Two epidemiologic studies observed the effects of the co-twin’s sex in opposite directions (9, 35), although the inconsistency may be due to the difference in the age of women included in these studies.

In summary, twinship, as well as zygosity and the co-twin’s sex, may affect breast cancer risk. However, data on prenatal estrogen levels do not necessarily support a hypothesis that higher estrogen concentrations contribute to an increased breast cancer risk.

Preeclampsia and other pregnancy complications. Women with preeclampsia have reduced estrogen levels and elevated testosterone levels (47). In two nested case-control studies, Ekbom et al. (7, 37) found that preeclampsia and eclampsia were associated with a reduction of 76 and 59 percent, respectively, in the breast cancer risk of the daughter. One of these studies (37) also found an increased risk of breast cancer (OR = 3.96, 95 percent CI: 1.45, 10.81) associated with premature birth (gestational age less than 33 weeks). These results were adjusted for age, birth date, and selected maternal and birth characteristics but not for reproductive history of the daughter. The only other study that examined the effects of pregnancy complications suggested an increase, although not statistically significant, in the breast cancer risk of the daughter associated with the broad category of pregnancy complications (OR = 2.20, 95 percent CI: 0.86, 6.22) or preeclampsia alone (OR = 3.46, 95 percent CI: 0.86, 13.90) (36).

Timing of births. Janerich et al. (32) showed that women born to a mother whose first birth occurred 3 or more years after the mother’s marriage had a higher breast cancer risk (OR = 1.45, 95 percent CI: 1.18, 1.78) than women born to a mother whose first birth occurred within 3 years of her marriage, after adjustment for age at first birth and parity of the daughter. This variable may be a surrogate measure of the parents’ fertility, but its relation to sex hormone levels during pregnancy is not clear.

Season of birth. Yuen et al. (48) noted that the month of birth might be related to the risk of breast cancer; Swedish women born in June had a 5 percent higher risk than those born in December. However, two other studies conducted in New York State (26) and Japan (49) did not support the seasonal pattern in the distribution of breast cancer cases. It is possible that the effect of birth season is observable only in the areas with a large summer-winter contrast in day length.
sunlight exposure, and food supply. Nevertheless, the association seems to be weak, if it even exists, and the role of sex hormones in such an association remains to be shown.

**Race/ethnicity.** Large variations in breast cancer incidence across countries and among racial/ethnic groups in the United States have been well documented (50). In California, age-adjusted incidence rates of breast cancer are the highest among non-Hispanic White women, followed by Blacks, Hispanics, and Asians (51). Prenatal estrogen levels do not follow the trend predicted by the hypothesis that breast cancer rates have higher estrogen levels. Henderson et al. (52) reported higher serum levels of testosterone, estradiol, and free estradiol for Black women than for White women prior to week 12 of their first pregnancy. Lipworth et al. (53) showed that maternal plasma levels of estradiol, estriol, prolactin, progesterone, and SHBG at week 16 were significantly higher in Chinese women than in Caucasian women. No ethnic differences in the umbilical cord blood levels of dehydroepiandrosterone sulphate, estradiol, total testosterone, free testosterone, or SHBG were found in a study of 125 neonates in New Zealand (54).

**Maternal smoking during pregnancy.** Smoking during pregnancy reduces maternal levels of circulating estrogens. Bernstein et al. (55) showed that estradiol levels in pregnant women who smoked were 18 percent lower than those in nonsmokers, after adjustment for gestational age. Petridou et al. (39) also found lower maternal estrogen levels in smokers, but the difference was smaller; total estrogen levels in smokers were 91 percent (90 percent CI: 80-103 percent) of the levels in nonsmokers. Epidemiologic data on the effect of maternal smoking during pregnancy on the daughter’s breast cancer risk are mixed. Sanderson et al. reported a slightly increased risk associated with maternal smoking (OR = 1.3, 95 percent CI: 0.9, 2.1 (adjusted for subject’s age and menopausal status)) for women aged 50-64 years and OR = 1.9, 95 percent CI: 0.9, 3.8 (adjusted for birth weight) for women aged 30

### TABLE 1. Results from epidemiologic studies on the association between twinship and breast cancer risk*

<table>
<thead>
<tr>
<th>Author(s) (reference no.)</th>
<th>Study population (country)</th>
<th>Effective no. of subjects†</th>
<th>Odds ratios or risk ratios (point estimates and 95% confidence intervals) for twinship</th>
<th>Matching variables</th>
<th>Covariates adjusted for in analysis‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerhan et al. (9) (2000)</td>
<td>United States</td>
<td>1,230 NA§</td>
<td>Twin: 1.00 (reference)</td>
<td>NA</td>
<td>1–10</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Monzygotic: 1.04 (0.43, 2.50)</td>
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<td></td>
<td></td>
<td></td>
<td>Dizygotic: 1.77 (1.16, 2.70)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Female co-twin: 1.82 (1.20, 2.75)</td>
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<td></td>
<td></td>
<td></td>
<td>Male co-twin: 1.49 (0.80, 2.78)</td>
<td></td>
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<tr>
<td>Weiss et al. (35) (1997)</td>
<td>United States</td>
<td>2,150 1,961</td>
<td>Twin: 1.00 (reference)</td>
<td>Age, geographic region</td>
<td>1, 3–5, 7, 9, 11–16</td>
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<td></td>
<td></td>
<td></td>
<td>Monzygotic: 1.39 (0.7, 2.6)</td>
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<td></td>
<td></td>
<td></td>
<td>Dizygotic: 2.06 (1.0, 4.5)</td>
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<tr>
<td>Ekbom et al. (37) (1997)</td>
<td>Sweden</td>
<td>1,068 2,727</td>
<td>Twin: 1.00 (reference)</td>
<td>Birth date, hospital at birth</td>
<td>17–23</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Monzygotic: 0.36 (0.08, 1.73)</td>
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<td></td>
<td></td>
<td></td>
<td>Dizygotic: 1.72 (0.92, 3.20)</td>
<td></td>
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<tr>
<td>Sanderson et al. (33) (1996)</td>
<td>United States</td>
<td>1,134 1,380</td>
<td>Age at diagnosis, 21–45 years</td>
<td>Age, county of residence</td>
<td>1, 15, 24</td>
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<td></td>
<td></td>
<td></td>
<td>Singleton: 1.0 (reference)</td>
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<td></td>
<td></td>
<td>Twin: 0.6 (0.3, 1.3)</td>
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<td></td>
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<td></td>
<td>Age at diagnosis, 50–64 years</td>
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<tr>
<td>Braun et al. (44) (1995)</td>
<td>Sweden</td>
<td>740 NA§</td>
<td>Singleton: 1.0 (reference)</td>
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<td>1, 25</td>
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<td></td>
<td></td>
<td></td>
<td>Twin: 0.9 (0.4, 2.2)</td>
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<tr>
<td>Standfast (26) (1967)</td>
<td>United States</td>
<td>229 NA</td>
<td>Monzygotic twin: O/E§ = 1.0</td>
<td>NA</td>
<td>None</td>
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<td></td>
<td></td>
<td></td>
<td>(0.9, 1.2)</td>
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<td></td>
<td>Dizygotic twin: O/E = 1.1 (1.0, 1.2)</td>
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</table>

* Sorted by year of publication in reverse chronologic order.
† Number of subjects included in statistical analyses for the effects of twinship.
‡ 1, age; 2, education; 3, family history of breast cancer; 4, age at menarche; 5, age at first term pregnancy; 6, height; 7, body mass index; 8, waist-to-hip ratio; 9, alcohol intake; 10, hormone replacement therapy; 11, race; 12, study site/study cohort; 13, previous breast biopsy/personal history of benign breast disease; 14, number of children/parity; 15, menopausal status; 16, number of mammograms in the 5 years before the reference date; 17, maternal age; 18, maternal socioeconomic status; 19, maternal preeclampsia or eclampsia; 20, neonatal jaundice; 21, severe prematurity; 22, birth weight; 23, maternal parity; 24, maternal smoking; 25, calendar year of cancer diagnosis.
§ NA, not applicable (study design other than case-control study); O/E, observed-to-expected ratio.

* Epidemiological data on the association between twinship and breast cancer risk.*

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years or less) (33). Weiss et al. (35) did not observe as strong an effect, although the confidence intervals of the odds ratios from the two studies overlapped (OR = 1.06, 95 percent CI: 0.8, 1.4). The findings of Sanderson et al. may have been confounded by other risk factors for breast cancer that were not taken into account in statistical analysis.

Lifestyle factors. Prenatal estrogen levels have been studied in relation to maternal dietary habits, alcohol consumption, and coffee drinking during pregnancy. On the basis of dietary data collected at week 26 of pregnancy by using a semiquantitative food frequency questionnaire, Petridou et al. (56) found no association between any food group or nutrient and maternal plasma levels of total estrogens, estradiol, or estriol. In the same study, weight gain up to week 31 of pregnancy showed a nonsignificant positive correlation with total estrogens and estradiol (56). The authors of the study speculated that total caloric intake, as reflected in weight gain, might be a more important determinant of sex hormone levels than composition of the diet. Serum estradiol levels at week 26 were higher in alcohol drinkers and lower in coffee drinkers, after adjustment for maternal age, maternal weight, parity, tobacco smoking, and the association between coffee drinking and alcohol consumption (57). To our knowledge, no data are available that relate these lifestyle variables of the mother during pregnancy to breast cancer risk of the daughter.

Summary

Experimental data on rodents support the hypothesis that exposures to high estrogen levels and a high dietary fat intake during the perinatal period increase breast cancer risk in the female offspring, possibly because of their long-term effects on the morphology and physiology of the mammary gland epithelium. Some epidemiologic data suggest that higher maternal age at birth and twin membership may be associated with an increased breast cancer risk, but the results are inconsistent across studies. Higher prenatal estrogen levels in twin pregnancies further support the sex hormone hypothesis, but breast cancer risk associated with zygosity (monozygotic vs. dizygotic twins) and with sex of the co-twin does not follow the predictions based on estrogen levels. Complications during pregnancy may also be related to breast cancer risk of the daughter, but potential confounding by other risk factors has not been ruled out. Birth rank, which has been consistently correlated with prenatal estrogen levels in humans, was associated with breast cancer in only one (6) of the four studies.

PROSTATE CANCER

Hypothesized biologic mechanisms (figure 1, A)

Development and growth of the prostate during the perinatal period are dependent on androgens produced by the fetal testes, beginning at about week 8 of gestation (4). The ductal network in human prostates originates from solid epithelial outgrowths, called prostatic buds, at about week 10–12 of gestation (4, 58, 59). As discussed below, animal experiments have shown that estrogens modulate the development of prostate glands as well.

Experimental data support the hypothesis that perinatal steroid hormone exposure influences the structure and function of prostate glands. For instance, vom Saal et al. (60) showed that elevated serum free estradiol levels in male mouse fetuses led to the increased number of developing prostatic glands during fetal life. Perinatal exposure to estradiol and other estrogenic compounds induces epithelial and stromal hyperplasia (61), increases the relative weight of the prostate (18), and increases the incidence of prostate inflammation in adulthood (62). Male rats positioned in utero between female fetuses, which have been found to have higher estradiol levels and lower testosterone levels than male siblings placed between two male fetuses (45, 46), had a significantly larger cross-sectional area of developing prostatic epithelial buds than the latter did (45).

Developmental asynchrony of the prostate gland, reflected in persistent morphologic heterogeneity of the organ, was one of the characteristic observations in a mouse model of prostate carcinoma (63). Foci and segments that retain a prepubertal appearance were also observed in the prostates of young adult men (64). These morphologically abnormal prostate tissues may respond abnormally to hormonal stimuli (63). Interestingly, persistent prepubertal glands were rarely found in prostates of young adult men in China, where prostate cancer incidence rates are much lower than in Caucasian and African-American populations (63).

Perinatal estrogen treatment also may influence prostate carcinogenesis by inducing alterations in hormone receptors and the steroid feedback system (65). For instance, a 50 percent increase in serum free estradiol in male mouse fetuses resulted in a twofold increase in the number of prostatic androgen receptors per cell in adulthood (60). In rodents, neonatal exposure to estrogens leads to permanent alterations in the response of the prostate to androgens during adulthood (66). Other mechanisms by which perinatal sex hormones may affect prostate cancer risk are changes in the endogenous levels of hepatic enzymes that activate or detoxify carcinogens (67) and aberrant DNA methylation in the promoter regions of estrogen-responsive genes that may influence expression of those genes (68).

Interpretation of the findings regarding the morphology and function of prostate glands warrants caution. Some of the morphologic abnormalities in the prostate induced by maternal estrogens during the fetal period, such as squamous metaplasia and hyperplasia of glandular and stromal tissues, gradually regress 1–4 weeks after birth (59, 69). Furthermore, certain morphologic changes in rat prostates were prominent in that part of the organ that corresponded to the anatomic region of human prostate in which benign prostatic hyperplasia occurs (45). Prostate cancer in humans occurs mostly in the peripheral zone of the organ, while benign prostatic hyperplasia occurs in the inner periurethral region, called the transition zone (70). Therefore, observations in the animal model may be less relevant to carcinogenesis than to nonmalignant prostatic conditions, although it is possible that prostate cancer and benign prostatic hyperplasia share risk factors.
Experimental data (figure 1, B)

Experimental work on animal models of prostate cancer has been limited because of the rarity of spontaneous prostate tumors in most nonhuman species and differences in prostate anatomy and histopathology between rodents and humans (65, 71). Perinatal estrogen exposure causes epithelial dysplasia and carcinomas in the prostate and the male accessory sex glands of mice (65). High dietary fat intake during pregnancy may increase the prostate cancer risk of the male offspring, possibly because of the effect on androgen levels. Kondo et al. (72) investigated the effects of pre- and postnatal exposure to a high-fat diet on prostatic carcinogenesis in ACI/Seg rats that have a high incidence of spontaneous prostate cancer. At age 100 weeks, the male offspring in the high-fat diet group had a significantly higher prevalence of atypical hyperplasia of the prostate (73 percent) than their counterparts in the low-fat diet group (20 percent). The prevalence of adenocarcinoma was also higher, although not significantly so, in the high-fat diet group (20 percent) than in the low-fat diet group (0 percent). In addition, the mean serum level of testosterone was higher in the high-fat diet group than in the low-fat diet group at both 60 and 100 weeks of age (72).

Epidemiologic data (figure 1, C and D)

Epidemiologic data on perinatal characteristics and prostate cancer risk are also limited. The relation of pregnancy and birth characteristics to perinatal androgen levels is not well known. Since estrogens seem to play as important a role as androgens in the prenatal development of the prostate, data on correlates of estrogens reviewed in the Epidemiologic Data section of the breast cancer portion of this review may be relevant to the sex hormone hypothesis for a prenatal origin of prostate cancer.

Parental age at birth. In a study by Janerich et al., increasing age of the mother and of the father were each related to a reduction in prostate cancer risk (30) (for a 10-year differential, OR = 0.71, 95 percent CI: 0.52, 0.98 for maternal age and OR = 0.55, 95 percent CI: 0.41, 0.74 for paternal age). When both variables were included in a statistical model simultaneously, however, the effect of only paternal age remained statistically significant (OR = 0.40, 95 percent CI: 0.26, 0.62). The effect of paternal age was stronger in men less than age 65 years. Two other case-control studies (10, 73) showed no association between maternal age and prostate cancer risk. These studies did not examine the effect of paternal age. The finding of Janerich et al. regarding paternal age needs corroboration by additional epidemiologic studies and support from evidence on possible biologic mechanisms.

Birth weight. In a study of 62 male babies, Simmons et al. reported an inverse association between cord blood estradiol level and the infant’s birth weight (Spearman’s correlation coefficient, r = -0.32) (40). In the same study, birth weight was inversely associated with SHBG levels (r = -0.33) and positively associated with dehydroepiandrosterone sulphate levels (r = 0.27).

In a cohort study of 366 Swedish men born in 1913, Tibblin et al. observed a five- to sixfold increase in incidence rates of prostate cancer among men in the 76th–100th percentile of birth weight compared with men in the lowest 10th percentile (74). This association is one of the strongest found for perinatal characteristics and prostate cancer risk. However, the finding should be interpreted with caution because it was based on a small number of cancer cases (a total of 21 men). Furthermore, two case-control studies also conducted in Sweden showed no association between birth weight and prostate cancer risk (10, 73).

Pregnancy complications. Reduced estrogen levels and increased testosterone levels were found in pregnant women with preeclampsia when compared with those without the condition (47). In a case-control study by Ekbom et al. (10), a history of preeclampsia or eclampsia during pregnancy was associated with a significantly decreased incidence of prostate cancer in the male offspring (OR = 0.00, 95 percent CI: 0.00, 0.71). Another case-control study by the same investigators (73) also found a nonsignificant reduction in prostate cancer among men whose mothers had preeclampsia or eclampsia when those men were in utero (OR = 0.33, 95 percent CI: 0.07, 1.45).

In one of these studies (10), premature birth (gestational age less than 35 weeks) was associated with a decrease in both mortality and the incidence of prostate cancer. Ekbom et al. (73) also reported a reduction in prostate cancer risk associated with longer duration of gestation (OR = 0.94, 95 percent CI: 0.89, 0.99 for each 1-week increase in duration) after adjustment for placental weight. However, the odds ratio estimates were closer to unity after adjustment for the newborn’s body size (weight or length) at birth instead (73), making it difficult to determine which variable has more direct relevance to prostate cancer risk.

Other variables. In a study of 21,226 male twins in Sweden, no elevation in prostate cancer risk was found in association with being a twin when compared with the national population (observed-to-expected ratio = 1.0, 95 percent CI: 0.8, 1.1 for monozygotic and dizygotic twins) (44). In a study by Maccoby et al. (42), testosterone and estradiol levels in the cord blood were higher in firstborn than in later-born males (0.297 vs. 0.266 ng/ml for testosterone, 8.89 vs. 6.87 ng/ml for estradiol). Janerich et al. (30) reported no association between birth rank and prostate cancer risk, although detailed results were not reported.

Summary

Data on perinatal variables and prostate cancer risk from both experimental and epidemiologic studies are sparse. Exposure to high estrogen levels and a high dietary fat intake during the perinatal period seems to affect the development and physiology of the prostate of the male offspring in rodents. In humans, parental age, birth weight, and complications during pregnancy may be associated with prostate cancer risk, but currently available epidemiologic evidence is based on a small number of studies. The limited data available do not support the relation of twinship or birth rank to prostate cancer risk.
CONCLUSIONS

Epidemiologic data currently available on the associations between perinatal attributes and the risk of breast and prostate cancers in adulthood are circumstantial at best and often inconsistent among studies. Even for the few prenatal variables for which associations with cancer risk have been suggested, data on the relation of those variables to sex hormone levels are either sparse or inconsistent with the hypothesis that the prenatal origin of breast and prostate cancers is explained by variation in sex hormone levels. Although some experimental studies support the biologic merit of the link between prenatal sex hormone exposure and cancer risk in adulthood, it is not clear whether such evidence can be extrapolated to humans.

Challenges in addressing the link between perinatal sex hormones and cancer risk in humans are multiple. First, the putative induction period spans many decades, making prospective cohort studies almost out of the question. Furthermore, increasing trends in breast and prostate cancer incidence over the last few decades make it difficult to compare older studies with more recent ones. The long induction period also adds to the second challenge, that is, confounding by risk factors during childhood, puberty, and adulthood. Perinatal attributes could simply be predictors of socioeconomic status (11, 12) or behavioral and biologic factors in later stages of life that might have a more direct influence on cancer risk. The possibility of confounding and bias would not necessarily be excluded, even if biologic markers (e.g., serum sex hormone levels) during the perinatal period were correlated with cancer risk. Third, our uncertainty about causal mechanisms and lack of knowledge about the “relevant” timing of exposure (38) prevent development of markers of a “biologically effective dose” (75) in the target organ or of intermediate outcomes. Moreover, while such variables as the number of stem cells susceptible to malignant transformation sound plausible in concept, they would not be practical to measure in human studies.

Limitations in testing the hypothesis directly and comprehensively lead to alternative methods of investigation. Identification of indicators of perinatal estrogen levels in cross-sectional studies, followed by examination of those indicators in association with cancer risk either at the population level (ecologic studies) or individual level (case-control or cohort studies), would help to evaluate the plausibility of sex hormones as mediators (5). Studies of migrants and multiethnic populations whose cancer risk varies would provide another source of aggregate data regarding early life environment. Examination of perinatal characteristics and their association with known cancer risk factors in adolescence (e.g., age at menarche) might also help us to better understand the web of events in different phases of life. Such studies can be performed in a shorter time than it would take to follow up infants for cancer outcomes. Alternatively, if biologic specimens from the perinatal period were not needed, data on perinatal characteristics could be collected retrospectively. Several studies on correlates of prenatal sex hormone levels (38-43, 47, 52, 53, 55-57) have already been conducted. However, current data do not provide strong enough evidence to favor sex hormones over other factors as a plausible explanation regarding the associations between perinatal variables and cancer risk observed in epidemiologic studies. Alternative explanations other than sex hormones (e.g., growth factors) may be as compatible with the associations between perinatal variables and breast and prostate cancer risk as is the sex hormone hypothesis (11, 12, 76-78).

Clearly, epidemiologic studies alone will not be able to answer all of the questions relevant to the hypothesis. Experimental models remain an essential complement for elucidating steps involved in biologic mechanisms linking perinatal exposures to adulthood cancers. Although estrogens and androgens are reasonable candidates because of their roles in the development and functions of the breast and prostate, the merit of sex hormones as prenatal antecedents of breast and prostate cancers must be evaluated against that of other possible explanations.

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