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Examining Breast Cancer Growth and Lifestyle Risk Factors: Early Life, Childhood, and Adolescence

Elizabeth H. Ruder¹, Joanne F. Dorgan², Sibylle Kranz¹, Penny M. Kris-Etherton¹, and Terry J. Hartman¹

¹Department of Nutritional Sciences, The Pennsylvania State University, University Park

²Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, PA

Abstract

The perinatal period, childhood, and adolescence are important intervals for breast cancer risk development. Endogenous estrogen exposure is thought to be highest in utero, and exposure to estrogens throughout life plays an important role in increasing breast cancer risk. Some evidence suggests that breast tissue is not fully differentiated until after the first full-term pregnancy; thus, breast tissue might be more susceptible to carcinogenic influences during early life and adolescence. Birth characteristics of the daughter, including gestational age, birth weight, and birth length are associated with maternal hormone levels during the index pregnancy, and birth size has been related to daughter's timing of puberty and adult breast cancer incidence. Furthermore, early life and adolescence are critical times for maturation of the hypothalamic pituitary ovarian axis, which regulates production of ovarian hormones including estrogen and progesterone. Childhood height, growth, diet, and body mass index (BMI) have also been associated with breast cancer risk later in life. Of the examined characteristics, we conclude that the available evidence is suggestive of a positive relationship of breast cancer risk with birth weight, birth length, and adolescent height, and an inverse relationship with gestational age and childhood BMI, although several inconsistencies exist in the literature. The best evidence for a relationship of adolescent diet and adult breast cancer risk is indirect, and the relationship of diet, weight status, and weight gain in childhood deserves further attention. The interaction of birth characteristics with established risk factors over the life course, such as age at menarche, in addition to gene-environment interactions, require more research. Further study is also needed to clarify the biologic mechanisms influencing the observed associations.

Keywords

Birth weight; Body mass index; Estrogen; Gestational age; Gonadal steroid hormones; Menarche

Introduction

The risk of breast cancer increases with age with approximately 80% of breast cancer diagnosed in women aged > 50 years.¹ Exposure to estrogens throughout life plays an important role in increasing breast cancer risk,^{2,3} and endogenous estrogen exposure is hypothesized to be highest in utero.⁴ Inasmuch, there is growing interest in the relationship of fetal and early-life characteristics, including diet and growth, as an antecedent for later development of breast cancer. Early life and adolescence are critical times for maturation of the hypothalamic pituitary ovarian (HPO) axis, which regulates the production of ovarian hormones including estrogen

and progesterone.⁵ Unlike most organs, the majority of breast development occurs during puberty under the influence of these hormones. Some evidence suggests that breast tissue is not fully differentiated until after the first full-term pregnancy,⁶ and therefore early life might be a period in which the breast is more highly susceptible to carcinogenic influences. Infant birth size is positively associated with maternal hormone levels during pregnancy,⁷⁻¹⁰ maternal diet,¹¹ daughter's pubertal timing,¹² and incidence of breast cancer later in life.¹³⁻¹⁵ Other childhood and adolescent characteristics related to growth are also likely to have an influence. The interactions of the intrauterine hormonal milieu, postnatal development and later disease risk are clearly complex, and the biologic mechanisms underlying the relationship are not fully understood. This review summarizes the literature examining the influence of gestational age, birth weight, birth length, childhood growth, diet, and body mass index (BMI) on later development of adult breast cancer risk.

Gestational Age

Infants born at both extremes of gestational age have been hypothesized to be at increased risk of breast cancer because of increased exposure to hormones in utero. Whereas infants born > 40 weeks gestation experience a prolonged exposure to pregnancy hormones, available data suggest that maternal hormones are higher in pregnancies that end prematurely. Wu and colleagues reported significant inverse correlations between maternal serum estradiol and estriol at 16 and 27 weeks gestation with ultimate duration of the pregnancy in white and Chinese women ($P < .01$ for all comparisons).¹⁶ Mazar et al similarly reported higher maternal plasma and amniotic fluid estradiol concentrations at 32-36 weeks among women who delivered prematurely.¹⁷ However, concerns have been raised about the validity of maternal serum estrogen measures as a proxy for fetal exposure because of lack of correlation with umbilical cord levels^{18,19} and variation in plasma volume expansion in pregnancy.²⁰ Still, female infants' urinary estrogen excretion on the day of birth decreases with increasing gestational age from 28 to 41 weeks.²¹ Thus, although imperfect, available data indicate that, while a longer gestation results in prolonged exposure of the fetus to hormones of pregnancy including elevated estrogens, maternal (and possibly fetal) estrogen concentrations are higher in pregnancies that are of shorter duration.

Linked birth-cancer registry data generally suggest an increased risk of breast cancer among pre-term infants, although results are not totally consistent across all studies (Table 1).^{14, 22-25,28-30} In the prospective Uppsala (Sweden) Academic Hospital birth cohort 1915-1929, infants of a given birth size who were born at 30-38 weeks (the shortest gestation category) were at a significantly increased breast cancer risk before age 50 years (relative risk [RR], 2.10; 95% CI, 1.05-4.21) compared with those born at ≥ 41 weeks gestation (the longest gestation category; $P = .03$).¹⁴ Similarly, in a large, age-matched, population-based, case-control study in Sweden that linked birth records with cancer registry data, breast cancer risk was inversely associated with gestational age,²² and stratification by menopausal status did not substantially alter the results. Women born at ≤ 33 weeks gestation were almost 4 times more likely to develop breast cancer compared with those born at > 33 weeks (odds ratio [OR], 3.96; 95% CI, 1.45-10.81).²² Comparable results were reported in a smaller study of women born in Stockholm from 1925-1934.²³ However, in another small record linkage study conducted in Sweden, no association of gestational age (≤ 32 weeks or 33-34 weeks compared with > 35 weeks) with breast cancer was seen.²⁴ Moreover, a protective effect of prematurity (gestational age < 33 weeks vs. ≥ 37 weeks; adjusted OR, 0.11; 95% CI, 0.16-0.79) was reported in a record-linkage study of American women.²⁵ Cases in the American study were < 37 years of age at diagnosis, which might suggest an etiology different from most breast cancer cases. A protective effect of short gestation is also supported by a case-control study that compared the birth records of 87 Swedish female twin pairs wherein one twin developed breast cancer with twin pairs wherein neither twin developed breast cancer. However, the analysis was not

stratified by zygosity, and because dizygotic twins are exposed to 2 placentas in utero, their hormone exposure is higher compared with monozygotic twins or singletons.²⁶ In addition, monozygotic twins typically have a shorter gestation than dizygotic twins,²⁷ and pairs in which one twin develops breast cancer might be less likely to be monozygotic compared with pairs in which neither twin develops breast cancer. Stratifying the analyses by zygosity could aid in the interpretation of results and understanding the relationship of gestational age and breast cancer risk.

Studies based on mothers' reports of birth characteristics generally report no association of pre-term delivery with breast cancer risk. No association was found between breast cancer risk and mother's recall of the index daughter's gestational age among daughters < 45 years of age at diagnosis living in Washington state.²⁸ A case control study nested within the Nurses' Health Studies (NHS) I and II also obtained birth characteristics retrospectively from subjects' mothers.²⁹ Prematurity was ascertained by asking if the daughter was premature and how early the birth had been (< 2 weeks, 2-4 weeks, > 4 weeks). Prematurity of any degree was not associated with breast cancer risk. The analysis was adjusted for current age, but did not stratify by menopausal status at breast cancer diagnosis because of small numbers and inadequate statistical power.

In summary, 3 cohort studies with record linkage^{14,22,23} suggest an inverse relationship between gestational age and breast cancer risk, although case-control studies that rely on recall of gestational age,^{28,29} a record-linkage study with women diagnosed at a very young age²⁵ or who were twin births,³⁰ and one small cohort study²⁴ found either a null relationship^{24,28,29} or a positive association of gestational age and breast cancer risk.^{25,30} Numerous possible explanations for the dissimilar results exist. Foremost is questionable accuracy of self-reported and maternal recall of gestational age.³¹⁻³³ This potential error leads to misclassification of exposure which, when non-differential between cases and controls, generally biases results to the null. Recall accuracy declines with time since index birth,³¹ although mothers' recall might be more accurate in their recall if the index infant was born < 36 weeks gestation compared with infants born full term.³³ Another issue is the wide variety of categorization schemes of gestational age and prematurity. Furthermore, few studies ascertain other health conditions during the index pregnancy, such as pre-eclampsia, which is associated with shorter gestation³⁴ and may be associated with lower maternal estrogen production.³⁵ Moreover, the low survival rate of pre-term infants before the creation of neonatal intensive care units might differentiate the pre-term infants who survived to adulthood and were at risk of developing breast cancer. Given the inconsistent results and disparate characteristics of the study populations (including very early breast cancer diagnosis and twin births) it is not possible to draw strong conclusions about the association of gestational age with breast cancer risk. Nonetheless, the better well-designed studies support an inverse relationship between gestational age and breast cancer risk. Additional work is needed to determine whether the inverse relationship of gestational age and breast cancer risk is strongest among premature births versus those near term but of comparatively shorter gestation.

Birth Weight

Birth weight is known to be positively associated with maternal sex hormones, including estradiol⁷⁻¹⁰ and insulin-like growth factor I (IGF-I)^{36,37} during pregnancy. Sex hormones and IGF-I have both been implicated in the initiation and promotion of breast cancer.^{2,3,38-42} Birth weight has been related to the timing of puberty and incidence of breast cancer in adulthood.^{12-15,25,30,43-45} Therefore, birth weight could be a proxy for in utero hormonal exposures that affect breast cancer risk in adulthood. Although recorded birth weights are preferred, maternal recall of birth weight years after the index birth is reasonably valid.^{31,32,46,47} A recent review and metaanalysis by Michels and Xue⁴⁸ provides a comprehensive

review of the literature relating to birth weight and breast cancer risk, indicating an overall increased breast cancer relative risk (combined pre- and post-menopause) of 23% (95% CI, 13%-34%) for women with higher birth weights (mostly above 4000 g) compared with lower birth weight (mostly below 2500 g), and readers should refer to this report for a detailed analysis. We will present only a brief overview of the most salient studies.

Numerous studies describe a positive association of birth weight and breast cancer risk, particularly among pre-menopausal breast cancer cases.^{13,25,29,30,49-52} Pre-menopausal breast cancer risk linearly increased with increasing birth weight in a nested case-control study within the 2 cohorts of the NHS.²⁹ Birth records of 2176 women (including 59 breast cancer cases) from the Medical Research Council (MRC) National Survey of Health and Development 1946 Birth Cohort in Great Britain indicated birth weight ≥ 4000 g increased age-adjusted pre-menopausal breast cancer risk (RR, 5.03; 95% CI, 1.13-22.47) compared with women weighing < 3000 g at birth ($P = .03$).⁴⁹ However, as reflected by the wide confidence interval, the estimate of the magnitude of the association lacked precision because of the small numbers of cases. Nevertheless, medical records for 373 Norwegian breast cancer cases and 1150 control women⁵⁰ also suggested breast cancer risk was positively associated with birth weight. The OR for women whose birth weight was in the highest (≥ 3730 g) versus the lowest (< 3090 g) quartile was 1.4 (95% CI, 1.1-1.9; $P = .02$). A matched case-control study that linked New York State birth and tumor registry data of women < 37 years at diagnosis ($n = 484$)²⁵ and a case-control study using cancer-registry data and self-reported birth weight of women < 45 years at diagnosis ($n = 746$)¹³ describe increased breast cancer risk at the low and high ends of the birth weight spectrum, but associations were significant only for high birth weight.

Although most of the published work examining the relationship between birth weight and breast cancer risk suggests a positive association, some studies find no relationship. Ekbom et al.²² failed to find a statistically significant association of breast cancer risk with birth weight or birth length among members of one case-control study nested within a Swedish cohort, although, as noted previously, gestational age was inversely associated with breast cancer risk among cohort members. Two other studies report that the effect of birth weight was no longer apparent after adjustment for birth length or head circumference,^{14,53} suggesting potential multicollinearity. No association of birth weight and pre-menopausal breast cancer risk was detected in the Shanghai Breast Cancer Study (OR for birth weight > 4000 g, 0.7; 95% CI, 0.4-1.4 compared with birth weight 2500-2999g).⁴³ Small sample sizes at the extremes of birth weight might have been insufficient to detect an effect. Also, Asian populations exhibit a narrower birth weight distribution compared with non-Hispanic whites,⁵⁴ which might contribute to the null findings in Asian ethnic populations.^{43,55}

In summary, the evidence supporting a positive association of birth weight and breast cancer risk is moderately strong, and it is generally more apparent among pre-menopausal women.^{13,15,45} As with gestational age, the possibility of a survival bias of the low birth weight infants and possible unreliable retrospective reports of birth weight and the combined effects of other birth size variables could influence the results.

Birth Length

Birth length is associated with adult height,⁵⁶ which in turn has been positively related with adult breast cancer risk.^{57,58} Length at birth is a stronger predictor of adult height than weight at birth,^{59,60} and like higher birth weight, a longer length at birth might be a proxy for prolonged in utero estrogen and growth hormone exposure,¹⁹ which potentially increases future breast cancer risk (Table 2).^{14,50,53}

Research to date generally supports a positive association of birth length with breast cancer risk. In the previously discussed Uppsala birth cohort,¹⁴ risk of incident breast cancer < 50

years of age was > 3 times higher among women in the highest compared to the lowest quintile of birth length (RR, 3.40; 95% CI, 1.5-8.0; $P < .001$) after adjustment for gestational age. However, birth length is highly correlated with birth weight and head circumference,⁶¹ and further adjustment for these characteristics attenuated the association between birth length and breast cancer risk such that trends no longer achieved statistical significance ($P = .09$ and $P = .12$ for birth weight and head circumference, respectively). Unlike the association observed for early age at onset of breast cancer, there was no evidence of an association between birth length and breast cancer risk in older women.

Two studies conducted in Norway similarly report positive associations between birth length and breast cancer risk. The first was a case-control study where birth length was abstracted from medical records of cases and age-matched controls.⁵⁰ Compared with the lowest quartile of birth length (< 50 cm), women in the highest quartile (≥ 51.5 cm) at birth were at increased risk for developing breast cancer (OR, 1.4; 95% CI, 1.1-1.9; $P = .02$). Results were adjusted for age at first birth and parity, but not birth weight, and results were not stratified by age at diagnosis. The second study, conducted by the same author,⁶² was a prospective study of a 16,016 member Norwegian cohort with birth data abstracted from hospital records. A total of 312 breast cancer cases were observed over 40 years of follow-up. Women ≥ 53 cm at birth were at a 1.8-fold (95% CI, 1.2-2.6) increased risk of developing breast cancer compared with women < 50 cm at birth ($P = .02$). Adjustments were made for birth year, length of gestation, birth order, maternal age, maternal marital status, and maternal socioeconomic status at childbearing. After stratification by age at diagnosis (< 50 or > 50 years) and adjustment for the aforementioned variables plus birth weight and head circumference, the RR of breast cancer < 50 years was 1.5 (95% CI, 0.8-2.9) for women with birth length ≥ 53 cm compared with < 50 cm at birth. Breast cancer risk among women ≥ 50 years at diagnosis was also increased among the group with the longest length at birth, but not significantly (RR, 2.1; 95% CI, 0.9-5.0).

The evidence for a positive relationship between length at birth and breast cancer risk appears strong. Potential reasons for some of the discrepant findings could arise from the difficulty in obtaining accurate length measurements in infants. In addition, measurements are frequently recorded to the nearest 0.5 cm, thus reducing precision and variability. In addition to racial/ethnic differences, the effect of genetics must be considered in future investigations. A recent analysis of genetic effects on birth weight, length, and gestational age concluded that 31% of normal variation in birth weight and birth length and 11% of normal variation in gestational age was explained by inherited genetic factors.⁶¹ It is also possible that polygenic factors control birth size and disease risk,⁶³ and this interaction deserves further attention. Recent work to identify the quantitative trait loci for birth weight and birth length might help to identify specific genetic variants and further refine this relationship.⁶⁴ Additionally, ≥ 1 analysis¹² suggests that girls born short-heavy reach menarche later compared with peers born long-light. This finding, in addition to supporting the importance of characterizing birth size in > 1 dimension to capture the collective effect of birth size, highlights the importance of understanding intermediate risk factors for potential incongruence over the life course. In this example, high birth weight is associated with later menarche, although early menarche is an established breast cancer risk factor. Although beyond the scope of this review, it is thought that growth and body weight mediate the relationship.^{65,66}

Childhood Height and Linear Growth

The positive association of birth length and adult height have been previously referenced,⁵⁶ but growth through childhood to final adult height deserves further attention. Adult height is positively associated with breast cancer risk.⁵⁸ Adult height is also positively associated with age at menarche, or otherwise stated, girls who have menarche late are on average taller adults.

⁶⁷ This association appears incongruent with evidence that early menarche is also an established risk factor for breast cancer.⁶⁸ The biologic rationale for this late menarche-taller adult height relationship lies in that skeletal growth typically reaches completion approximately 2 years after menarche.⁶⁹ On average, girls who are taller than their peers as children tend to reach menarche earlier,^{70,71} but stop linear growth earlier, leading to a post-pubertal crossover in average height for different age-at-menarche groups.⁷² Another key to understanding this complex relationship with breast cancer risk might rest in childhood growth velocity and the timing of childhood growth spurts. This suggests a multifaceted connection, and growth velocity might be central to understanding the seemingly contradictory relationship between age at menarche and adult height in relation to breast cancer risk (Table 3).^{51,71-73}

Ahlgren et al⁵¹ modeled individual growth curves from 8 to 14 years of age for 117,415 Danish women with information on birth weight and annual height and weight measurements linked to the Danish Cancer Registry. After mutual adjustment for birth weight, height at age 8 years, BMI at age 14, and age at menarche, age at peak growth was inversely associated with breast cancer risk. Each year delay in age at peak growth was associated with a decrease in RR of 0.94 (95% CI, 0.91-0.97), and results did not differ materially when analyses were stratified by age at diagnosis. Moreover, regardless of age at diagnosis, each 5-cm increase in height from age 8 to age 14 years was associated with increased breast cancer risk (RR, 1.17; 95% CI, 1.09-1.25).

Analyses from the prospective MRC National Survey of Health and Human Development birth cohort analysis⁷² suggest that breast cancer cases are consistently taller than non-cases during childhood. Furthermore, after mutually adjusting for other components of growth, each one standard deviation (SD) increase in height velocity at ages 4-7 years increased the breast cancer OR by 1.54 (95% CI, 1.13-2.09), while a comparable increase at ages 11-15 years increased the OR by 1.29 (95% CI, 0.97-1.71). Associations of growth velocity were stronger for women with earlier menarche. When restricted to women with menarche < 12.5 years, each 1 SD increase in height velocity at ages 4-7 years and 11-15 years increased the breast cancer OR by 1.95 (95% CI, 1.25-3.04) and 1.66 (95% CI, 1.00-2.78), respectively. Thus the adverse effect of fast growth might be stronger among women with an early age at menarche.

Berkey and colleagues⁷³ also observed a positive association of adolescent peak height velocity (PHV) in an analysis of the NHS I. Annual height measurements were not available, but PHV was estimated using age at menarche, adiposity at age 10 years (assessed retrospectively with somatotype pictograph) and adult height. After multivariate adjustment, pre-menopausal breast cancer risk was positively associated with PHV. Among women in the highest quintile of estimated PHV (8.9 cm per year), risk of breast cancer was 1.31 compared with those in the lowest quintile (≤ 7.6 cm per year) with a significant trend observed across increasing categories of PHV ($P = .001$). Results were similar for post-menopausal breast cancer cases, the RR for PHV > 8.9 cm per year was 1.40 ($P = .001$).

In contrast, a case control study nested in a Swedish cohort that was constructed from birth and school health records in childhood with linkage to the National Hospital Discharge Registry and Death Registry⁷¹ failed to detect an association of PHV with breast cancer risk. Although breast cancer cases were significantly taller on average than controls at each age from age 7 years to age 15 years, the Z-score (a normalized measure of growth velocity) for change in height for each age from 7-15 years did not differ by case status. This finding contradicts that of the previously discussed Berkey et al⁷³ study which found a positive association of PHV with breast cancer risk. However, several differences in the studies exist which make a direct comparison difficult, including that Berkey et al's characteristics were extrapolations on available data. Additional research examining growth velocity using prospectively collected data and adjustment for potential breast cancer confounders is warranted, and widespread

calculation of Z-scores or other normalized measure would aid in comparison across studies.
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Overall, the available data suggest that growth patterns appear less influential than maximal height attainment on breast cancer risk. However, growth velocity and patterns at different ages during childhood should not be disregarded. Growth patterns in relation to breast cancer risk remain a new area of inquiry and further developments will help to clarify the relationship, such as the relative importance of increased height velocity at specific ages. These factors might be useful in understanding the pathway to risk, and could offer important contributions to understanding a complex disease process.

Diet in Early Life and Adolescence

In animal models, maternal high-fat diet during pregnancy is associated with increased estradiol in the mother and increased incidence of induced mammary tumors in first generation offspring.⁷⁵ To date, no published investigations of maternal diet and subsequent breast cancer risk in human offspring are available although several investigations of childhood and adolescent diet have been conducted. A recent metaanalysis of 11 studies on the history of having been breastfed concluded no effect on breast cancer risk⁷⁶ and will not be reviewed in detail.

In a case-control study nested in the NHS I and II, Michels and colleagues⁷⁷ investigated the relationship between pre-school diet and breast cancer risk. Nurses' mothers completed a 30-item Food Frequency Questionnaire (FFQ) of their daughter's diet at ages 3-5 years. After adjustment for numerous confounders, regular consumption of french fries was associated with increased risk of breast cancer (OR, 1.27 for 1 additional serving per week; 95% CI, 1.12-1.44). Although recall bias is possible, the authors note that if unhealthful items were recalled more often by the case mothers, it would be expected that other foods generally deemed unhealthy also would have been associated with an increased risk of breast cancer. Future research of preschool diet patterns with breast cancer risk among a cohort of children followed prospectively could help identify the true nature of the relationship.

Analyses from the NHS cohort I similarly indicated a possible relationship between adolescent diet and adult breast cancer risk.⁷⁸ Cases and controls selected from the cohort completed a 24-item FFQ reflecting their dietary intakes at ages 12-18 years. Higher consumption of eggs (RR, 0.82 per increase of 1 egg per day; 95% CI, 0.67-0.99) and vegetable fat (RR, 0.85 for highest quartile compared with lowest quartile; CI not reported; $P = .05$) were associated with a reduced breast cancer risk after multivariate adjustment, whereas consumption of butter was positively associated with risk (RR, 1.06 per increase of 1 patient per day; 95% CI, 1.00-1.13). Little difference in the RR was detected following stratification by menopausal status at diagnosis. Incident breast cancer was diagnosed between 1976 and 1986, and adolescent diet was assessed in 1986 when participants were 40-65 years old; thus bias might have been introduced by inaccurate recall, particularly if it was differential in cases and controls. In a related study, 47,355 participants in the NHS II aged 34-51 completed a 131-item FFQ regarding their diets during ages 12-18 years.⁷⁹ At the time of diet recall, breast cancer cases were postdiagnosis, resulting in potential for recall bias as with the earlier NHS study. Albeit, increased intake of vegetable fat and vitamin E were both found to be protective against breast cancer diagnosis, but when vitamin E and vegetable fat were entered simultaneously in the model, only vitamin E upheld its significance. In vitro evidence indicates that vitamin E succinate (an ester of vitamin E) induces apoptosis in breast cancer cells,⁸⁰ and the study authors⁷⁹ speculate that similar activity might be important during remodeling of the terminal end buds during adolescence. Higher glycemic index diets during adolescence were also positively associated with higher breast cancer risk (RR, 1.47 for highest vs. lowest quintile;

95% CI, 1.04-2.08; $P = .01$) in the present analysis. High glycemic index diets might increase serum glucose and insulin which in turn increases late post-prandial secretion of IGF-1.³⁸ IGF-1 concentration has been positively associated with premenopausal breast cancer risk in the NHS Cohort I,⁴² but no association was detected in the NHS Cohort II with no obvious explanation for the discrepancy.⁸¹ Issues related to the retrospective diet recall and possible recall bias, as with the earlier NHS diet investigation, remain.⁷⁸ One smaller ($n = 172$)⁸² and 1 larger ($n = 1647$)⁸³ US-based case-control study also failed to detect a clear relationship of retrospectively recalled adolescent diet and adult breast cancer risk, including early-onset breast cancer.⁸³

Soy isoflavones genistein and daidzein are highly concentrated in soy foods and have possible cancer protective effects.⁸⁴ Shu and colleagues⁸⁵ analyzed data from the population-based Shanghai Breast Cancer Study in which soy intake at ages 13-15 years was ascertained through a 17-item FFQ. Breast cancer cases reported lower soy intake during adolescence (6.45 g soy protein per day for cases versus 7.23 g per day for controls; $P = .002$); differences were highly significant for both pre- and post-menopausal women. The authors suggest that soy food intake in adolescence might explain some variability in breast cancer incidence among white and Asian populations, as well as explain increasing incidence among Asian-Americans who adopt a Western-style diet. For comparison, it is estimated that soy intake is 13 to 80 times higher in China than in select European countries and the United States.⁸⁶⁻⁸⁸ However, in the present study, similar to the NHS, which relied on recall of adolescent diet after breast cancer diagnosis, there is potential for bias.

Because of difficulties inherent in directly evaluating associations of childhood and adolescent diet with breast cancer in adulthood, Dorgan et al evaluated the effect of adolescent diet on serum hormones that influence breast development and are associated with breast cancer in adulthood.⁸⁹ In that study, which was a randomized controlled trial to evaluate the effects of a reduced fat diet at 8-17 years of age, participants in the intervention arm had lower serum estrogens and progesterone during follow-up compared with those in the usual care arm. These findings are consistent with a possible influence of adolescent diet on breast cancer risk. Thus, although direct evidence for an association of early-life or adolescent diet with breast cancer risk is weak, indirect evidence is consistent with such an association. Lack of clarity from studies that have attempted to directly assess the association might be due to errors in recall of adolescent or early-life diet decades later. Prospective studies are needed to clarify the relationship.

Body Mass Index

In adults, pooled analyses indicate BMI is inversely associated with breast cancer risk among pre-menopausal women, but positively associated with post-menopausal breast cancer risk.⁵⁷ It has been suggested that weight gain, particularly weight gain since age 20 years, might be a stronger determinant of post-menopausal breast cancer risk than absolute BMI at a single point in time.⁹⁰ The relationship of childhood and adolescent BMI with adult breast cancer risk is similarly complex.

Ahlgren et al⁵¹ investigated BMI among 141,393 Danish girls, born between 1930-1975 with school health records linked to the Danish Cancer Registry. Body mass index was inversely associated with breast cancer risk, with each 1-unit increase in BMI from ages 8 to 14 corresponding with an RR of 0.96 (95% CI, 0.93-0.99) after adjusting for attained age. At age 14 years, individuals in the highest quintile of BMI had a breast cancer RR of 0.84 (95% CI, 0.75-0.94) compared with those in the lowest quintile. However, the median BMI in the highest quintile was 22.4 kg/m² and might not be reflective of the adiposity in contemporary populations. The inverse association of BMI at 14 years of age was independent of birth weight,

age at peak growth, age at menarche, height at age 8, and height increase between ages 8-14 years and did not differ by menopausal status at diagnosis. Thus, the effect of childhood obesity on breast cancer does not appear to be a result of acceleration of puberty brought about by adiposity.

An inverse association of childhood and adolescent BMI with breast cancer was also observed in the 1946 MRC National Survey of Health and Development British birth cohort.⁷² In that cohort, women who subsequently developed breast cancer were consistently thinner from ages 2-15 years than women who remained breast cancer free. Cases also experienced a faster decrease in BMI between ages 2 and 4 compared to non-cases. Women with more dense breasts are at an increased risk of breast cancer, and after adjusting for BMI at the time of mammography and childhood, BMI was inversely associated with mammographic density in this cohort.⁹¹ Thus, one mechanism by which childhood BMI could potentially influence breast cancer risk is via effects on mammographic density.

In contrast, perceived weight at 15 years of age was not associated with breast cancer risk in the Shanghai Breast Cancer Study. However, the Shanghai study used a retrospective self-report of adiposity whereas the previous studies had prospective measurements of weight and height. Additionally, the previous studies were conducted among predominantly white populations living in Europe and the BMI distribution in Asians is different from that of whites, which might be a factor in the discrepant findings.

In general, the evidence indicates increased adiposity in childhood might protect against later pre- and post-menopausal breast cancer risk. However, in the studies reviewed, adiposity typically refers to the highest category of the study population. Given that many of the cohorts were born in the 1940s or earlier, the degree of adiposity was likely less severe than the obesity observed in upper percentiles of contemporary pediatric populations. Future work should examine the existence of BMI threshold values for breast cancer risk. Caution should be heeded before using such findings to construct a public health message.

Conclusion

Breast cancer is an etiologically complex disease. Additional work is needed to clarify how known and proposed breast cancer risk factors influence risk. Although there are inconsistencies in the literature, gestational age appears to be inversely related with breast cancer risk, whereas birth weight and birth length appear to be positively associated. Adult height is positively associated with breast cancer risk, but the relationship might be mediated by height velocity with fast growth early in life, increasing overall breast cancer risk. The evidence regarding childhood diet is limited and inconclusive, but child and adolescent BMI appear to be inversely related with breast cancer risk.

Birth characteristics tend to be highly correlated, and multicollinearity might hinder the ability to detect independent effects. Other issues in the current literature include lack of conformity in controlling for covariates and potential confounders, including familial breast cancer history and parity. In addition, the majority of work has been conducted in non-Hispanic white and Asian populations, with little available evidence from other racial/ethnic groups. Furthermore, much of the prospectively collected data is derived from cohorts born in an environment with different lifestyle trends than experienced today. These issues could affect the relevance of the research in the current environment.

Most of the available evidence supporting a relationship between birth characteristics and in utero hormone exposure is based on measurements of maternal plasma hormone concentrations which might not be reflective of fetal concentration in the cord blood^{18,19}; similarly, the stress of labor might alter cord blood concentrations differently than maternal serum concentrations.

Additional work is needed to clarify the true relationship. In the interim, the underlying hypothesis that the associations of birth size and gestational age with breast cancer risk manifest from in utero estrogen exposure should be considered speculative while the research continues and other explanations for the relationship are pursued.

Directions for future work should aim to connect the relevance of risk factors over the developmental spectrum. The association of adolescent diet and breast cancer, specifically within the context of BMI and dietary quality, has not been extensively investigated. This is an area of particular public health interest given that diet is amenable to change. Furthermore, research aimed at clarifying apparently contradictory relationships of early life and adolescent characteristics with breast cancer risk could provide insights into the underlying cause of the disease. Prospective studies beginning in utero with the outcome of breast cancer are the ideal study design for clarifying these relationships. As early-life risk factors become better understood, individuals and families might make lifestyle choices to minimize risk. Furthermore, given the etiologic complexity of breast cancer, understanding early-life risk factors plays an important role in unraveling disease development.

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Table 1
Selected Studies on the Association of Gestational Age and the Risk of Breast Cancer

Study	Study Design	Birth Year	Number of Cases [*]	Gestational Age Categories [†]	OR/RR/SIR [*] (95% CI)	P Value	Covariate Adjustment
Ekblom et al (1997) ²²	Population-based, case-control nested in cohort [‡]	1874-1961	1068 ³	≤ 33 Weeks vs. > 33 weeks	3.96 (1.45-10.81)	—	Matched on age and date of birth, adjusted for birth characteristics, including birth weight and maternal pre-eclampsia.
Ekblom et al (2000) ²³	Cohort [‡]	1925-1934	7 ¹ 5 ²	< 31 Weeks vs. ≥ 35 weeks	6.7 (1.4-19.5)	—	Standardized using age, sex, and time-specific cancer incidence rates
Hubinette et al (2001) ³⁰	Population-based, case-control [§]	1886 - 1958	87 ³	40 Weeks vs. < 33 weeks	8.4 (1.3-54.4)	—	Matched on person-years at risk of developing breast cancer and birth year within 9 years
Innes et al (2000) ²⁵	Population based, case-control [‡]	1958 -1981	484 ¹	< 33 Weeks vs. ≥ 37 weeks	0.11 (0.16-0.79)	.05	Race, birth weight, and birth characteristics, including maternal pre-eclampsia
Kajiser et al (2003) ^{24//}	Cohort [‡]	1925-1949	19 ¹ 39 ³	≤ 34 Weeks vs. > 35 weeks	1.13 (0.68-1.77) ¹ 0.99 (0.40-1.35) ³	—	Standardized using age, sex, and time-specific cancer incidence rates
McCormack et al (2003) ¹⁴	Cohort [‡]	1915-1929	63 ¹ 296 ²	30-38 Weeks vs. ≥ 41 weeks	2.10 (1.05-4.21) ¹	.03	Ponderal Index, proxy measures of adult life risk factors
Michels et al (1996) ²⁹	Population-based, case-control nested within 2 cohorts [¶]	1921-1965	550 ³	> 4 Weeks premature vs. not premature	1.04 (0.46-2.38)	—	Adult life risk factors
Sanderson et al (1998) ²⁸	Population-based, case-control [¶]	1945-1947	510 ¹	< 37 Weeks vs. 37-42 weeks	0.9 (0.5-1.8)	—	Matched on age and county of residence; adjusted for birth weight and adult life risk factors

Abbreviations: OR = odds ratio; RR = relative risk; SIR = standardized incidence ratio

^{*} Menopausal status: ¹(≤ 50 years), ²(≥ 50 years), ³(both age groups).

[†] Referent listed second, only highest and lowest categories are listed where P value is indicated.

[‡] Data obtained from birth records linked to cancer registry.

[§] Data obtained from Swedish Twin Registry.

// Includes cases from Ekbom et al 2000.

// Data obtained from maternal recall of birth characteristics and medically confirmed breast cancer diagnosis.

Table 2
Selected Studies on the Association of Birth Length and the Risk of Breast Cancer

Study	Study Design	Birth Year	Number of Cases	Birth Length Categories / (cm; Referent Listed Second)	RR/OR (95% CI)	P Value	Covariate Adjustment
McCormack et al ¹⁴	Cohort [‡]	1915-1929	63 ¹ 296 ²	≥ 52.5 vs. ≤ 49	2.59 (0.90-7.47) ¹ RR for postmenopausal risk NS, but values not reported	.09	Gestational age, birth weight, proxy measures of adult life risk factors
Vatten et al (2002) ⁵⁰	Population-based case-control [‡]	1910-1970	373 ³	≥ 51.5 vs. ≤ 50	1.3 (1.0 -1.8)	.02	Matched on age, birth date, city of residence at the time of diagnosis; adjusted for parity and age at first birth
Vatten et al (2005) ⁵³	Cohort [‡]	1920-1958	167 ¹ 145 ²	≥ 53 vs. ≤ 50	1.8 (1.2-2.6) ³	.02	Year of birth, length of gestation, birth order, maternal age at childbearing, marital status, and maternal socioeconomic status

Abbreviations: NS = not significant; OR = odds ratio; RR = relative risk

* Menopausal status: ¹(< 50 years), ²(≥ 50 years), ³(both age groups).
[‡] Only highest and lowest categories are listed.
[#] Data obtained from birth records linked to cancer registry.

Table 3
Selected Studies on the Association of Childhood Height/Linear Growth

Study	Study Design	Birth Year	Number of Cases*	Relationship Measured	OR/HR (95% CI)	P Value	Covariate Adjustment
Ahlgren et al ¹	Cohort [†]	1930-1975	3340 ⁴	Risk of breast cancer with each year delay in age at peak growth	0.94 (0.91, 0.97) ³	.03 [‡]	Birth weight, height at age 8 years, BMI at 14 years, adjustment for age at menarche did not appreciably change the estimates
				Risk of breast cancer with each 5-cm increase in height from age 8 to 14 years	0.90 (0.86, 0.95) ²		
					0.98 (0.93, 1.03) ³		
Berkey et al ³	Cohort [§]	1921-1946	806 ⁰ 1485 ¹	RR of peak height velocity > 8.9 cm	1.17 (1.09, 1.25) ⁴	.001	Age in 1976 or age at menopause; peak height velocity; adiposity at ages 5,10, and 20 years; other adult life risk factors
					1.15 (1.05, 1.27) ²		
					0.94 (0.92, 0.97) ³		
De Stavola et al ²	Prospective cohort	1946	59 ⁴	Odds of developing breast cancer with each one standard deviation increase in height velocity:	1.31 (CI = NR) ⁰	.001	Height, height velocity at other ages, BMI, BMI velocity Age at first birth, interval between birth, parity, social class, and BMI did not substantially alter results
				From age 4 years to age 7 years	1.40 (CI = NR) ¹		
				From age 11 years to age 15 years	1.54 (1.13, 2.09)		
Hilakivi-Clarke et al ^{7/1}	Cohort	1924-1933	42 ² 135 ³	HR of breast cancer for height in highest quintile at ages:	1.29 (0.97, 1.71)	.01	Unadjusted
				7 Years	1.9 (1.1, 3.1) ⁴		
				15 Years	1.9 (1.2, 3.2) ⁴		
				Mean height of breast cancer cases taller than mean height of controls at each age from 7 to 15		<.05	
				Z-score change in height for each age from 7 to 15 years not significantly different		NS, P value NR	

Abbreviations: BMI = body mass index; HR = hazard ratio; OR = odds ratio; NR = not reported; NS = not significant; RR = relative risk; SIR = standardized incidence ratio

* Menopausal status: 0(premenopausal), 1(< 50 years), 2($\geq$ 50 years), 3(both age groups), 4(postmenopausal).
[†] Height data obtained from health records linked to cancer registry.
[‡] P value represents difference in risk ratio according to attained ages.
[§] Growth data obtained from self-reported retrospective report and medically confirmed breast cancer diagnosis.
^{//} P trend across quintiles of increasing weight or growth.