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Breast cancer risk accumulation starts early – Prevention must also

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Abstract

Purpose—Nearly 1 in 4 breast cancers is diagnosed before the age of 50, and many early-stage premalignant lesions are present but not yet diagnosed. Therefore, we review evidence to support the strategy that breast cancer prevention efforts must begin early in life.

Methods—Literature review

Results—Exposures during childhood and adolescence affect a woman's long-term risk of breast cancer, but have received far less research attention than exposures that occur later in life. Breast tissue undergoes rapid cellular proliferation between menarche and first full-term pregnancy, and risk accumulates rapidly until the terminal differentiation that accompanies first pregnancy. Evidence on childhood diet and growth in height, and adolescent alcohol intake, among other adolescent factors are related to breast cancer risk and risk of premalignant proliferative benign lesions.

Conclusion—Breast cancer prevention efforts will have the greatest effect when initiated at an early age and continued over a lifetime. Gaps in knowledge are identified and deserve increase attention to inform prevention.

Introduction

A woman's risk of breast cancer is shaped by many different factors over the course of her life. Some of these factors — such as family history — cannot be modified, but many others are amenable to change. Much of the research on modifiable risk factors for breast cancer

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has involved exposures that occur at mid-life and beyond, but by focusing primarily on adult women, we miss the even greater impact on breast cancer prevention that could be achieved by acting much earlier in the course of breast development.

Roughly 24% of breast cancers are diagnosed before the age of 50[1]. Therefore, reducing breast cancer incidence in young women requires that prevention efforts begin much earlier in life. The effects of early life prevention, however, are not necessarily limited to premenopausal disease; some benefits extend across a woman's lifespan. In order to achieve the maximum reduction in both pre- and postmenopausal breast cancer, prevention efforts must begin early in life and be sustained. Modifiable risk factors at each phase of life contribute to woman's risk of breast cancer.

In this review, we discuss breast cancer prevention strategies that can be implemented early in life. We focus on childhood and adolescence; *in utero* exposures may also affect breast cancer risk [2], but are likely to be difficult to modify. We also discuss the relationship between early life growth and development and risk of breast cancer in order to provide additional evidence of the important and sustained effect that early life has on subsequent breast cancer risk. Some of the individual risk factors that we discuss have previously been the topic of systematic reviews, and we did not replicate these reviews; instead, we provide context for the important role of early life on breast cancer risk, bring together many of the disparate factors that have been evaluated, and identify some important remaining gaps in our knowledge. Optimal approaches to cancer prevention must incorporate the full range of modifiable risk factors.

In addition to early life strategies for breast cancer prevention, we discuss strategies for the prevention of premalignant benign breast disease (BBD). Proliferative benign breast disease increases a woman's risk of breast cancer [3] and efforts to reduce the occurrence of proliferative BBD are likely to augment cancer prevention efforts. Reflecting the complex multiple step process of genetic alteration for development of human cancers, long time periods are required for tumor progression to accumulate[4]. Accordingly, when BBD precedes a diagnosis of breast cancer, it does so by a median of roughly 10 years [5]. This further emphasizes the importance of prevention early in life.

Breast Cancer Burden

Breast cancer is the most commonly diagnosed type of cancer among women worldwide [6]. The incidence of breast cancer increases sharply with age beginning in the 20s, with a median age at diagnosis in the U.S. of 61 years [7]. Numerous lines of evidence point to the strong influence of lifestyle and reproductive patterns on the rising incidence of breast cancer as countries have moved from pre-industrial to post-industrial, or from low income to high income. Migrant studies of women who move from low-incidence to high-incidence countries, for example, demonstrate that breast cancer risk increases among the daughters of migrants [8]. Globally, breast cancer incidence tends to be highest in high-income regions such as North America, Northern and Western Europe, and Australia and New Zealand [6]. Incidence rates have traditionally been much lower in Asia and parts of Africa, but several Asian countries have experienced large increases in incidence among both younger and older women [9] [10] [11].

Well-established risk factors for breast cancer include reproductive factors such as early age at menarche, late age at first birth, nulliparity, and late age at menopause [12]; family history of breast cancer [13]; alcohol intake [14]; exposure to ionizing radiation [15]; use of combined estrogen plus progestin postmenopausal hormone therapy [16]; recent use of oral contraceptives [17]; physical inactivity [18]; and leanness in early life and obesity in later life [19,18].

Breast cancer is not a single disease, and our understanding of the heterogeneity of breast tumors has increased greatly in recent years. Molecularly defined subtypes of breast cancer have been identified [20,21], and these subtypes differ in their behavior and response to treatment [22]. The effects of some breast cancer risk factors also vary by tumor characteristics [23-25], and ongoing efforts to expand our understanding of subtype-specific etiology may suggest new approaches to prevention. Comprehensive prevention efforts, however, are unlikely to be implemented with only a single subtype of breast cancer in mind; given the burden that a breast cancer diagnosis places on a woman, prevention of any type of breast cancer remains an important goal.

Benign Breast Disorder

Benign breast disorders (BBD) are a heterogeneous group of histological entities, usually divided into non-proliferative lesions, proliferative lesions without atypia, and proliferative lesions with atypia.[26,27] Compared with non-proliferative BBD (which does not appear to increase the risk of breast cancer [28]), the relative risk of subsequent breast cancer is 1.3-1.9 for proliferative BBD without atypia and 4.1-5.3 for proliferative BBD with atypia. [29,26,30,3] Proliferative BBD is thus a well-confirmed risk marker of breast cancer risk, and may in some cases be a precursor of breast cancer [31]. See Figure 1 for a morphological model of breast cancer development.

BBD may be detected because of a palpable breast lump, through breast imaging, or as an incidental finding in tissue that has been removed for another reason [32]. Diagnoses of BBD increase with age, peak in mid-life, and then decline [33]. Factors that increase the risk of BBD include lean body fatness during childhood or adolescence[34], more rapid height growth [35], and alcohol intake [36,37]. Dietary factors such as vegetable protein, vegetable fat, peanut butter, and nuts, as well as carotenoids may reduce the risk of BBD in young women [38-40].

The Importance of Early Life Exposures

Age at menarche and peak height growth velocity are both related to breast cancer risk [41]. We discuss the role of childhood lifestyle factors and adiposity in relation to these markers of risk which have changed substantially with industrialization and our shift to urban living. In addition, breast tissue undergoes rapid cellular proliferation between menarche and first full-term pregnancy, and risk accumulates most rapidly until the terminal differentiation that accompanies first pregnancy. First pregnancy has both a short-term adverse effect on risk and a long-term reduction in subsequent risk accumulation [42]. The longer the interval between menarche and first pregnancy the greater is a woman’s breast cancer risk [43-45].

Therefore, menarche-to-first pregnancy represents a window of time when breast tissue is particularly vulnerable to carcinogenic stimuli [46].

Full term pregnancy induces cellular and molecular changes well documented in animal and human models [47]. Pregnancy induces decreases in the number of hormone-sensitive luminal cells and down regulation of the *Wnt* signaling pathway in basal stem and/or progenitor cells, making breast tissue less susceptible to carcinogens [48]. Using mammary epithelial cell subpopulations isolated from parous and age-matched virgin mice, reduced expression of *Wnt4* corresponded to a decrease in the proportion of *Wnt4*-secreting estrogen/progesterone receptor-positive cells. Recombinant *Wnt4* rescued the proliferation defect in vitro, supporting a causal link to parity-induced alterations of basal stem/progenitor cell properties and long-term protection from first pregnancy [49]. Sensitization of pro-apoptotic pathways particularly those mediated by p53 have been described [50] as have decreases in cells expressing nuclear p27 (encoded by CDKN2a) among parous women [51] adding further insights to pathways through which parity may decrease hormone responsive cells and reduce breast cancer risk. Additionally, first pregnancy induces long-term hormonal changes, including reduced prolactin and estrogen levels and increased levels of sex hormone-binding globulin, which may provide further protection against breast cancer [52,53]. Clearer understanding of these markers of cell dynamics may held identify pathways for prevention and markers of risk.

Early Life Energy Balance

Adiposity from Childhood to Adolescence

It is well established that adult adiposity is inversely related to premenopausal breast cancer and positively related to postmenopausal breast cancer [54]. Growing evidence indicates that adiposity in adolescence — measured or recalled at age 18 or 20 — shows a strong inverse relation to premenopausal breast cancer [55,56]. To understand childhood adiposity and breast cancer risk, numerous studies have used the Stunkard body figures (9 figure drawings that illustrate a range of body sizes from lean to obese) that perform well against measured childhood weight when recalled up to 30 years later [57,58]. In prospective studies, these measures of childhood and adolescent adiposity show persistence of the inverse relation with breast cancer into the postmenopausal years, even after controlling for adult attained weight or BMI [59]. Evidence points to this inverse relation persisting across subtypes of breast cancer defined by estrogen and progesterone receptor status and expression of ERBB2 (also known as HER2) [24]. Systematic reviews and meta-analyses show a dose-response inverse trend between late adolescent BMI and premenopausal breast cancer consistently observed across Caucasian and African heritages, though evidence from Asia is more variable [55].

The inverse relation with premenopausal breast cancer, described above, is also observed for proliferative BBD when relative adiposity at ages 5 and 10 are evaluated prospectively [34]. As seen for invasive breast cancer [45], the highest category of childhood adiposity has approximately 50% reduction in risk of proliferative BBD [34]. Together, these findings highlight the importance of exposures before menarche to the lifetime risk of both premalignant and malignant breast lesions. Mechanisms for the protective effect have been

explored and include alterations in clonal pools and altered estrogen, progesterone and prolactin levels [60,61] across pre- and postmenopausal years. Insulin pathways also show relations with childhood adiposity; among premenopausal women in the Nurses' Health Study II (median age 43.5 years), higher adiposity at ages 5 and 10 are each related to significantly lower insulin-like growth factor 1 (IGF-1) levels, but not growth hormone levels [62]. Further analysis, including data from women from the Nurses' Health Study and the Nurses' Health Study II (6520 participants with measured IGF-1 levels) showed that greater relative adiposity at ages 5 and 10 was inversely related to IGF-1 levels, as was BMI at age 18 [63]. These associations were also present for IGF binding protein 3 (IGFBP3). For both IGF-1 and IGFBP3 the associations were independent of adult BMI and menopausal status, suggesting a mechanism through which early life body size influences subsequent breast cancer risk. Effects of adiposity on breast density could also be important, but it remains uncertain whether childhood and adolescent adiposity affect breast density [64,65]. Adiposity may also act by reducing peak height growth velocity, as discussed below.

Peak Height Growth Velocity

Several studies have suggested that more rapid height growth during puberty may be a factor in the development of cancer. The rationale is that when childhood growth is more rapid, there is less time for repair of DNA damage caused by exposures to carcinogenic factors, and thus greater likelihood that permanent DNA damage will lead to cancer [66]. The first study attempting to relate peak height growth velocity (PHV (cm/yr), or maximum growth rate during the pubertal growth spurt) in girls to risk for breast cancer used a cohort study that did not directly measure adolescent growth [41]; the women in the Nurses' Health Study were age 30yr at baseline when they provided their adult height and recalled their age at menarche and their body fatness at ages 10yr and 20yr from Stunkard pictograms. The study authors then used data from a different longitudinal study[67], of girls followed from birth to adulthood with annual height and weight measurements along with age at menarche, to obtain a PHV prediction model that was then applied to the Nurses' Health Study data to estimate each woman's PHV. Participants in the top quintile (predicted PHV >8.9cm/yr) of peak height velocity had a 50% increase in risk of premenopausal and postmenopausal breast cancer compared to the lowest quintile (predicted PHV<7.6cm/yr), offering support to the hypotheses [41]. Two subsequent studies published in 2004 used data from cohorts that had measured heights and weights in childhood. A study of Danish women obtained annual heights and weights from school health records, and cases of invasive breast cancer from the Danish Cancer Registry; height growth from age 8 to 14yrs was significantly associated with breast cancer risk (relative risk (RR)=1.17/(5cm increase), 95% confidence interval (CI): 1.09-1.25), while growth during the peak year was marginally significant (odds ratio (OR)=1.15/(5cm increase), CI: 0.97-1.36) [68]. In a cohort of British girls, followed from birth in 1946 up through age 53yrs, height growth from age 4 to 7 years (OR=1.54/(1 standard deviation (SD) increase in height velocity), 95%CI: 1.13-2.09) and from age 11 to 15yr (OR=1.29/(1 SD increase in height velocity), 95%CI: 0.97-1.71) were associated with increased risk for breast cancer [69]. Because heights were measured at ages 7, 11, 15 years, and adulthood, the authors could not investigate PHV during the year of the growth spurt.

More recent evidence supporting the link between height growth velocity and breast cancer comes from a study of 3,926 American girls in the Growing Up Today Study (GUTS), who were ages 9-15yr at study initiation in 1996, with heights reported annually up through year 2001 and every two years thereafter. These females were followed into their 20's, as the first cases of BBD were being diagnosed. Those girls with more intense height growth spurts, PHV≥8.9cm/yr, were at increased risk for biopsy-confirmed BBD (OR=2.12, 95%CI: 0.90-5.00, p=0.09) relative to those whose peak growth was slowest [35]. When all reported BBD cases were analyzed, including those not confirmed by biopsy, girls growing most rapidly had significantly increased risk (OR=1.88, 95%CI: 1.04-3.41; p=0.04). The association was stronger among females with a family history of breast disease, though this may be due to more valid disease diagnosis information on those females.

Whether the rapid growth itself or related factors, such as dietary intakes or hormones that promote growth, are cancer initiators and/or promoters is still being explored. Childhood adiposity—which results in earlier onset of puberty in girls[70]—appears to reduce peak height growth velocity [67,71]. If adiposity, as early as age 3-5yr and up to age 10yr, leads to lower peak height growth velocity, then this pathway (originating in early childhood) provides lifelong differences in breast cancer risk observed for both pre and postmenopausal breast cancer [41]. Childhood diet (animal protein consumption as early as age 3-5yr) has also been related to earlier menarche and to higher peak height growth velocity [67], providing a mechanism through which early diet may exert influences on lifelong risk of breast cancer. However, more recent work on the GUTS cohort indicated that consumption of dairy products, even though they promoted rapid height growth [72], were not independently associated with risk for BBD [73], consistent with the pathway being through the growth velocity.

Age at Menarche

Earlier age at menarche is consistently linked with an increased risk of premenopausal and postmenopausal breast cancer [74]. In a meta-analysis of more than 100 epidemiological studies, each one-year decrease in age at menarche increased the risk of breast cancer by 5% [74]. The mechanisms underlying this relationship are not well understood, but may involve higher levels of estrogen both earlier [75] and later [76] in life in girls with earlier menarche. Estrogen is thought to promote the growth of estrogen receptor-positive (ER+) breast cancer, and may also have a role in the early development of ER+ and ER- breast cancers [77]. Two meta-analyses [74,78] and a large cohort study [79] found that age at menarche was associated with both hormone receptor-positive and hormone receptor-negative breast cancer, with one of the meta-analyses reporting a stronger effect on hormone receptor-positive cancer [78]. In a pooled analysis of breast cancer patients from 34 studies, early age at menarche was less common among cases with progesterone receptor-negative (PR-) breast cancer than among cases with PR+ breast cancer. In the Multiethnic Cohort Study, age at menarche was associated with ER+/PR+ breast cancer, but not with ER-/PR- breast cancer [80]. In addition to any effects mediated by estrogen or other hormones, early age at menarche could also increase breast cancer risk by lengthening the interval between menarche and first birth.

A relationship between age at menarche and risk of BBD has not been established, with several studies reporting null results [35,81]. Furthermore, age at menarche appears to have a weaker effect on breast cancer risk among women with BBD than among women without BBD [12,82]. One possible explanation, from the log-incidence model of breast cancer, is that risk accumulates before menarche for women who are on the path to developing BBD, contrasting with those women who do not develop BBD [12].

From the 19th century through the mid 20th century, average age at menarche declined steadily in the United States and Europe, possibly due to improved nutrition and a reduction in strenuous physical activity [83]. In the United States, average age at menarche declined from older than 14 years in 1877 to 12.8 years in 1947 [83]. In the UK, average age at menarche declined from 13.5 years among women born between 1908 and 1919 to 12.6 years among women born between 1945 and 1949 [84]. Age at menarche then appeared to stabilize in several developed countries [85,86], but studies of more recent birth cohorts suggest that it may once again be declining. Average age at menarche was 12.4 years among US girls born between 1980 and 1984 [87], and 12.3 years among UK girls born between 1990 and 1993 [84]. Age at menarche has declined substantially in rapidly developing countries. In Korea, for example, average age at menarche declined from 16.9 years among women born between 1920 and 1924 to 13.8 years among women born between 1980 and 1985 [88].

Age at menarche is determined in part by hereditary factors, but body size, nutrition and physical activity can also play a role [89]. Menarche tends to be earlier in girls with more body fat and later in girls who exercise [90]. A childhood diet that is high in animal protein and low in vegetable protein may also be linked with earlier menarche. [67]

Adolescent Lifestyle

Physical Activity

In a 2011 review by Lynch et al, the average reduction in breast cancer risk associated with physical activity at different ages was 16% for adolescence, 8% for early adulthood, 15% for middle adulthood, and 17% for age 50 and older [91]. In a 2007 review by Monninkopf et al, an inverse association between early physical activity and breast cancer was found in roughly half of the studies that had assessed physical activity before the age of 20 [92]. Some studies have reported that recent physical activity has a stronger effect than activity far in the past, but this could be due to more accurate reporting of recent physical activity [93].

Benefits of adolescent physical activity have been reported for both premenopausal and postmenopausal breast cancer, but it may be important to sustain physical activity into adulthood in order to obtain these benefits. In the Nurses' Health Study II, for example, a reduced risk of premenopausal breast cancer was most apparent among women who engaged in high levels of activity during both youth (ages 12-22) and adulthood; compared with women with low levels of activity during both age periods, active women had a 30% reduction in risk of breast cancer (RR=0.70, 95% CI: 0.53-0.93) [94]. Similarly, in the Shanghai Breast Cancer Study, the greatest reduction in risk of premenopausal and

postmenopausal breast cancer occurred in women who were physically active during both adolescence and adulthood [95].

Benefits of physical activity in youth may vary depending on the type, duration, and intensity of the activity. Although studies have differed in the type of information collected about physical activity, there is some evidence, primarily from studies in adults, that a higher intensity and longer duration of activity provide greater benefits [91]. A better understanding of the type of physical activity as a youth that maximizes cancer prevention could refine activity recommendations. Potential mechanisms by which physical activity may affect breast cancer risk include effects on sex hormones, insulin-related factors, or inflammation [96].

Alcohol

The International Agency for Research on Cancer (IARC) classifies alcoholic beverages as *carcinogenic to humans;* alcohol causes cancers of the female breast, oral cavity, pharynx, larynx, esophagus, liver, and colon and rectum [14].

Relatively few studies have evaluated the impact of alcohol intake at young ages on risk of breast cancer. Two prospective studies did not find a relationship between alcohol use before the age of 23 and risk of breast cancer [97,98]. Further analysis of one of these studies, however, focused on alcohol intake during the interval between two important reproductive events: menarche and first full-term pregnancy [99]. The relationship between alcohol intake during this interval and risk of breast cancer varied by the duration of the interval. Among women with a longer interval between menarche and first pregnancy (10 years or longer), each 10 g/day increase in alcohol intake increased the risk of breast cancer by 21%, independent of alcohol intake after first pregnancy. Among women with a shorter interval between menarche and first pregnancy, alcohol intake did not increase the risk of breast cancer. This suggests that a prolonged period of exposure at a stage when breast tissue is most vulnerable may increase the risk of breast cancer.

The limited available evidence also suggests an association between alcohol intake during adolescence and young adulthood and risk of BBD. In the prospective GUTS cohort, those who reported drinking 6 or 7 days per week at ages 16 to 23 had a more than five-fold increase in the risk of biopsy-confirmed BBD compared with those who never drank or drank less than weekly [36]. Information about histologic subtype of BBD was not available. Data from the Nurses' Health Study II show that increasing levels of alcohol intake prior to first pregnancy — but not after first pregnancy — increased the risk of proliferative BBD in women [99,37]. These findings, coupled with reports that adult alcohol intake does not increase the risk of BBD [100-102], suggest that early life alcohol intake has the greatest effect on these breast conditions. The effect of alcohol in adolescence and risk of BBD may be particularly strong for girls with a family history of breast cancer or a mother with BBD [103].

Several mechanisms have been proposed for alcohol's effects on the breast, but it's still unknown which, if any, explain the increased risk of BBD and breast cancer. Proposed

mechanisms include an effect on circulating hormone levels, production of carcinogens such as acetaldehyde, and oxidative stress [104].

Diet

Although migrant studies have pointed to early life exposures as important for breast cancer risk, the refinement of studies to address specific aspects of diet that may account for loss of protection with increasing number of generations in the US (and other high risk countries) have been pursued in few settings. Soy intake is the most extensively studied dietary component in childhood and adolescence. Perhaps the most compelling data come from studies of Asian migrants to Hawaii and the US mainland, where mothers recalled their children's diets for various childhood and adolescent age periods. Strong protection was observed for higher soy intake in childhood (OR 0.40), with weaker protection from intake during the adolescent (OR 0.80) and adult years (OR 0.76) [105].

A meta-analysis of 7 studies found that intake of high amounts of soy (20 mg per day of isoflavone) in Asian women was associated with a decreased risk for breast cancer, compared to Asian women consuming lower amounts (5 mg daily) [106]. A subsequent prospective study in Shanghai confirmed this protective association for adolescent soy intake at levels observed in Asian populations [107]. Of note, even the lowest intake of soy isoflavones in the Asian population was more than fivefold the "high" intake (0.8 mg per day) of women in Western countries, where studies have not shown a protective effect for soy. Together, these data indicate that in order to consider soy as a preventive agent for breast cancer, it will need to be consumed at very high levels (far above what is typical in Western populations), most likely starting early in life. On the other hand, soy may be a marker of vegetable protein intake; higher intake is related to later age at menarche in the Harvard Growth Study [67].

Several other aspects of adolescent and early adult diet have been studied in relation to risk of both proliferative BBD and invasive breast cancer. High fiber intake in adolescence is inversely related to risk of proliferative BBD in prospective studies, with significantly lower risk with high intakes in the range of values consumed by US adolescents [108]. In the Nurse's Health Study II we observed that women reporting intake of 27 grams of fiber per day or higher in adolescence had a relative risk of proliferative BBD of 0.62 compared to women consuming less than 15.1 grams of fiber per day [108]. However, in the same cohort, adolescent fiber intake was not significantly related to reduced risk of invasive breast cancer [109] after controlling for history of benign breast disease. A population-based case control study from Ontario on the other hand shows a strong inverse relation with adolescent dietary fiber, vegetable protein, and nut intake and invasive breast cancer risk [110].

Providing further evidence of protection conferred by adolescent diet, intake of nuts and peanut butter had strong inverse relations with BBD [108]. In the Nurses' Health Study II, higher nut consumption (1 or more servings of peanuts per week) was associated with 30% reduction in risk of proliferative BBD (95% CI 12% to 48%) compared with low nut consumption (less than one serving per month) [108]. In the GUTS cohort, nut or peanut butter consumption (at least 1 serving every three days) was associated with a 56% reduction in risk of biopsy-confirmed BBD (95% CI: 1% to 80%) compared with no

consumption [38]. This independent confirmation from two separate cohort studies, and the parallel apparent protection from nuts and soy (both legumes), raise important questions for vegetable protein, fiber, and diet composition in relation to possible pathways to prevention.

Replacement of animal protein with vegetable protein, before puberty, may lower peak height growth velocity[67], suggesting a mechanism for vegetable protein intake to protect against breast cancer. Based on dietary data (provided by mothers) of girls aged 3-5yr in the Harvard Longitudinal Studies of Child Health and Development [67], Berkey et al. estimated a significant reduction in peak height growth velocity for girls who would replace animal protein intakes with vegetable protein at ages 3 to 5. This diet substitution would also result in menarche occurring later. These dietary differences could explain the significantly lower risk of breast cancer, over the life course for women in the Nurses' Health Study, in the lowest peak height growth velocity group [41].

Other aspects of adolescent or childhood diet continue to provide contradictory evidence – milk intake is related to growth velocity and adult height [72] with a meta-analysis of controlled trials showing 0.4 cm growth per year for each 245 ml of milk daily [111]. However after controlling for growth velocity milk intake is not related to the risk of developing BBD (data from the Nurse's Health Study II [112] and GUTS [73]), or breast cancer [109]. The World Cancer Research Fund, in its 2010 Continuous Update for breast cancer, concluded that dietary components had limited or inconclusive evidence for both premenopausal and postmenopausal breast cancer [113], but ongoing research may alter those conclusions in the future.

Challenges to Studying Early Life Exposures

A clear challenge to studying early life risk factors for breast cancer is the long lag between exposure and diagnosis of breast cancer. For some other conditions that typically occur later in life, such as cardiovascular disease, several intermediate markers of risk (such as circulating lipid levels and blood pressure) are readily available and can provide an early surrogate of the disease outcome. No such easily assessed intermediate markers exist for breast cancer. Benign breast disease and breast density provide information about breast cancer risk, but BBD is not easily assessed, and information about breast density — based on mammographic findings — is typically only available for older women. This lack of intermediate markers limits the potential for short-term studies to evaluate interventions for breast cancer risk reduction.

To overcome the problem of the long time interval between exposure and outcome, many of the studies performed to date have been conducted in adult women, with retrospective recall of early life exposures. The validity of this approach is likely to vary by exposure, but evidence suggests that childhood and adolescent diet [114-116] and weight relative to others at age 5 and 10 [117,118] can be recalled with reasonable reproducibility and validity. Very long-term studies that include prospectively collected information about both early life exposures and breast cancer outcomes would help to address concerns about exposure misclassification, but are tremendously expensive and take decades to produce results. Using

existing studies and working to identify early-life biomarkers that predict breast cancer risk are likely to be more efficient strategies [2].

Research gaps

A woman's characteristics and behaviors during childhood and adolescence have emerged as important predictors of her later breast cancer risk (see Table). Some factors, such as age at menarche, are not easily modifiable, but those factors that are modifiable, such as physical activity, alcohol and diet, could form the basis for breast cancer prevention efforts. Continued research into unanswered questions about this phase of life (see Table 2) would also help to guide our efforts. The complex relationships between childhood adiposity and earlier menarche, but lower peak height growth velocity, and no overall relationship to adult height suggests that pathways for childhood and adolescent exposures may not all be captured adequately in classical analysis that controls for age at menarche. Perhaps reflecting this limit – comparison of incidence between a cohort of Chinese women and US rate of breast cancer showed that control for established reproductive risk factors including age at menarche, parity and so forth, as well as BMI, height, alcohol intake, accounted for only 70% of the difference in rates between countries. Perhaps the remaining "unexplained differences" relate to childhood diet and activity before menarche.

In its 2013 report, the Interagency Breast Cancer and Environmental Research Coordinating Committee recommended intensification of the study of chemical and physical factors that potentially influence the likelihood of developing or surviving breast cancer [119]. The report focused particularly strongly on chemical exposures. Endocrine disruptors and other environmental chemicals may affect breast development and risk of breast cancer, and research in this area continues [120].

The mechanisms by which early life characteristics and behaviors affect breast cancer risk are still not well understood, in spite of many plausible theories. This should not keep us from acting on promising prevention strategies; physical activity, for example, can be recommended without having a full understanding of how it affects the breasts, due to its clear health benefits overall, but further research in this area could suggest new risk reduction strategies. In the case of alcohol, identification of a mechanism may allow us to intervene in order to reduce the adverse effects of alcohol on the breast, or to identify women who are particularly susceptible to the adverse effects; genetic polymorphisms that affect alcohol metabolism, for example, may alter the effects of alcohol on the breast [104]. But again, encouraging adolescent girls to avoid alcohol can be recommended without a full understanding of mechanisms, due to the many other risks related to heavy consumption (binge drinking, driving while intoxicated, non-consensual sexual contact, etc.). In the case of both adolescent physical activity and drinking, because these behaviors tend to track into adulthood, modifying these behaviors during the teen years will likely result in more healthy behaviors in young women.

A better understanding of how early life factors affect subtypes of breast cancer is also important. If a risk factor only affects a relatively uncommon type of breast cancer (such as triple-negative breast cancer), studies that fail to take subtype into account may miss this

effect. Incorporating risk factors for rare subtypes into breast cancer prevention strategies may not have a large effect on the overall incidence of breast cancer, but could still provide an important benefit; triple-negative breast cancer, for example, is an important target for prevention efforts because it currently has a poor prognosis and few treatment options.

Early life factors also affect the risk of BBD, and consideration of how risk factors for BBD (and in particular, for proliferative BBD and atypia) overlap with those of breast cancer may provide clues to how breast cancer risk factors act. Some may act early in the process of carcinogenesis, affecting risk of both BBD and breast cancer; some may act later, affecting risk of breast cancer but not BBD; and some may have effects that vary by BBD status. Age at menarche, for example, is a well-established breast cancer risk factor, but does not affect the risk of BBD, and may have a weaker effect on risk of breast cancer among women with BBD than among women without BBD. The effect of age at menarche on risk of breast cancer may also vary by type of BBD [82]. A factor that affects risk of breast cancer but not BBD may either affect the progression of BBD to breast cancer, or the risk of breast cancers that arise independently of BBD. Clearly there are many complicated issues that require further research.

The key message is that breast cancer research and prevention efforts must continue to expand to include early life. Many prevention strategies are likely to have the greatest effect when initiated early in life and sustained. This could substantially increase the population benefit of prevention strategies. Studying childhood and adolescence in relation to diseases of adulthood is challenging, but studies conducted to date demonstrate that it is possible. Increased attention to this phase of life, coupled with further refinement and validation of the tools used to assess it, is necessary to achieve the full potential of breast cancer prevention. This is of vital importance not only for countries that already have high rates of breast cancer, but also for countries which are experiencing a rapid increase in rates as a result of social change.

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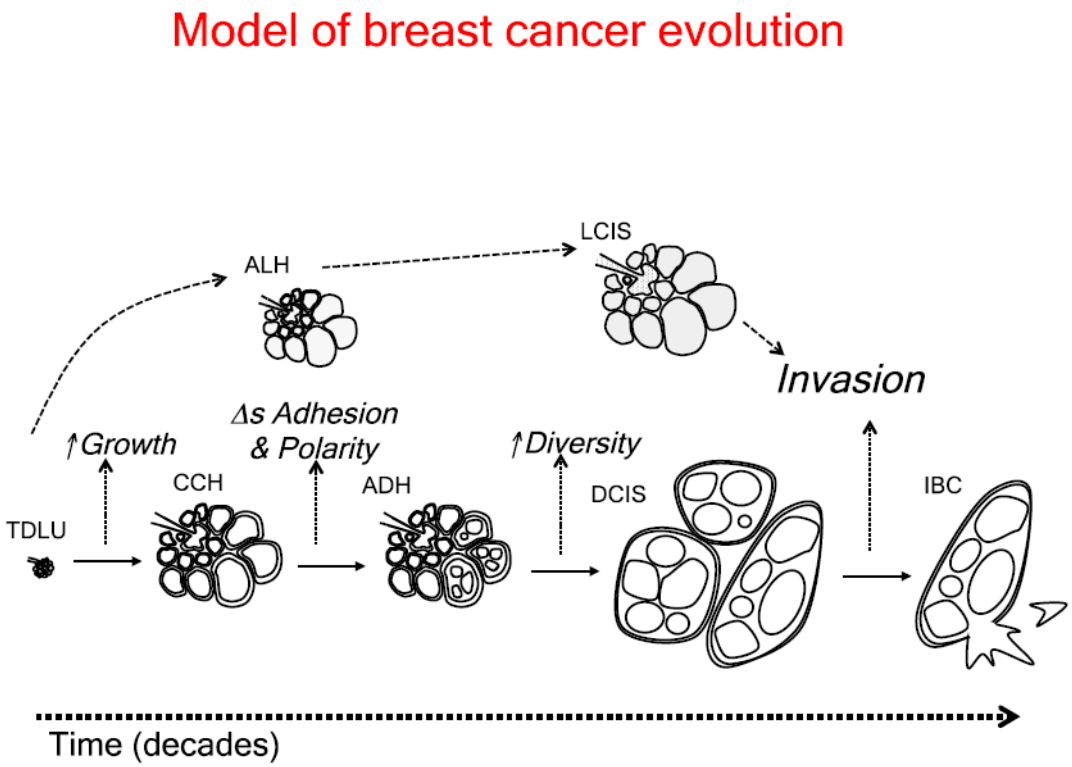

Figure 1.

A model for the development of invasive breast cancer (IBC) from normal terminal ductal-lobular units (TDLU) of the breast: In the upper pathway, atypical lobular hyperplasia (ALH)—a type of proliferative benign breast disease—is followed by lobular carcinoma in situ (LCIS) and IBC. In the lower pathway, columnar cell hyperplasia (CCH) progresses to atypical ductal hyperplasia (ADH)—a higher risk type of proliferative benign breast disease—and then to ductal carcinoma in situ (DCIS) and IBC.

Table 1

Early-life factors that influence risk of breast cancer

Premenopausal Breast Cancer		
Risk factor	**Exposure before menarche**	**Exposure after menarche and before first birth**
Greater adiposity	Substantially reduced risk	Substantially reduced risk
Diet: Soy/vegetable protein	Reduced risk*	Reduced risk*
Higher peak height growth velocity	Increased risk	NA
High physical activity	Unclear	Reduced risk†
Alcohol intake	NA	Increased risk
Postmenopausal Breast Cancer		
Greater adiposity	Reduced risk	Reduced risk
Diet: Soy/vegetable protein	Reduced risk*	Reduced risk*
Higher peak height growth velocity	Increased risk	NA
High physical activity	Unclear	Reduced risk†
Alcohol intake	NA	Increased risk

NA, not applicable

*A reduced risk of breast cancer occurs only at very high levels of soy intake (levels far above what is typically consumed in most Western countries)

†Physical activity that begins in adolescence and continues into adulthood may reduce risk to a greater extent that physical activity that occurs only during adolescence or only during adulthood.

Table 2

Unanswered questions about early life risk factors for breast cancer:

- Do early life exposures (diet, activity, adiposity) before menarche modify the short-term adverse effect of first birth? Do early life exposures from menarche to first pregnancy modify the short-term adverse effect of first birth?
- Does adolescent diet (fiber, vegetable protein, peanuts, soy, etc.) or alcohol, modify the rate of risk accumulation from menarche to first birth?
- Does higher peak height growth velocity explain international differences in breast cancer not fully explained by secular trends in age at menarche and parity?
- Does the reduced peak height velocity seen in children who had higher levels of adiposity at ages 5 and 10 convey the lifelong protection from this adiposity, and if so, can these mechanisms inform prevention strategies?
- Do components of in utero exposures or lifestyle before menarche drive increased risk of proliferative benign breast disease and other established intermediate endpoints (e.g., mammographic density)?
- How can we account for the problem of overdiagnosis when we evaluate potential preventive strategies?
- Are there reliable, early markers of breast cancer risk that can be used as surrogate outcomes in ongoing prospective studies of early-life exposures?
- Do the effects of early life exposures on risk of breast cancer vary across the molecularly defined subtypes of breast cancer? Can we identify new approaches to breast cancer prevention by focusing on uncommon but aggressive types of breast cancer?
- Do genetic polymorphisms modify the effects of breast cancer risk factors? Is it possible to identify those girls and women for whom avoidance of a particular risk factor is especially important?
- Do early life exposures induce morphologic (not including BBD) and/or molecular changes that make the breast more susceptible to cancer?
- Do early life exposures to modifiable factors affect lifelong breast cancer risk among women with family history of breast cancer?