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Review article

Identifying Opportunities for Cancer Prevention During Preadolescence and Adolescence: Puberty as a Window of Susceptibility

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A B S T R A C T

Purpose: Early life exposures during times of rapid growth and development are recognized increasingly to impact later life. Epidemiologic studies document an association between exposures at critical windows of susceptibility with outcomes as diverse as childhood and adult obesity, timing of menarche, and risk for hypertension or breast cancer.

Methods: This article briefly reviews the concept of windows of susceptibility for providers who care for adolescent patients.

Results: The theoretical bases for windows of susceptibility is examined, evaluating the relationship between pubertal change and breast cancer as a paradigm, and reviewing the underlying mechanisms, such as epigenetic modification.

Conclusions: The long-term sequela of responses to early exposures may impact other adult morbidities; addressing these exposures represents an important challenge for contemporary medicine.

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IMPLICATIONS AND CONTRIBUTION

This article provides an introduction for the concept of windows of susceptibility for health care providers with adolescent patients. It examines the developmental basis for associating early life exposures with adult disordering the paradigms of pubertal change and breast cancer and of biobehavioral susceptibility to environmental influences.

Over the past several decades, there has been an increasing awareness that early life events may shape developmental trajectories and thereby impact later health [1]. For example, adult diseases, such as breast cancer and ischemic heart disease, are believed to have origins in the early stages of life, and in recent years the study of breast cancer etiology has moved toward studying events during childhood [2]. Adolescence has

received little attention, despite the important behavioral, cognitive, and physical developmental changes that occur during this period. In this rapidly evolving area of study, several frameworks have been forwarded to explain these findings, incorporating diverse disciplines and perspectives that impact physical and mental health issues at the individual as well as public health level. These models are not mutually exclusive, yet often emphasize a specific perspective on antecedents or outcomes. This article will review briefly the literature that explores the factors in early life that impact the physiologic changes associated with puberty and how these influence adult morbidity using breast cancer as a paradigm.

Birth weight perhaps has been the most studied early life factor impacting later health. Both lower and higher birth weight, compared with normal, appear to have implications for short- and long-term outcomes across the life course. The impact of fetal

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undernutrition has been recognized for several decades. Observations of three cohorts—children born during the Dutch famine of 1944, born within the Hertfordshire (UK) district between 1911 and 1930, and selected from the Helsinki Birth Cohort of 1934–44—have led researchers to note the association between small size at birth and during infancy and later increased morbidity and mortality. The increased rates of adverse health outcomes included those for coronary heart disease [3–7]; stroke [7,8]; insulin resistance [9]; and type 2 diabetes mellitus [10]; adiposity [11,12], especially visceral fat distribution [13]; metabolic syndrome (associated with both low birth weight and maternal obesity [14]; and osteoporosis [15]. The increased rates led some early researchers to hypothesize the “thrifty phenotype” [10], often called the “Barker hypothesis,” as described below.

Nutritional excess during pregnancy has also been linked to adverse outcomes from childhood through adulthood, especially for development of obesity and type 2 diabetes [16]. Studies found that maternal triglyceride levels were associated with newborn weight [17] and that the strongest prenatal predictor of pediatric overweight and adiposity is maternal body mass index (BMI) [18]. Studies also found positive associations between birth size and cord insulin-like growth factor (IGF)-1 levels [19,20], as well as cord leptin levels [20], and between birth weight with adolescent height and lower age of menarche [21,22].

Developmental Plasticity

Observations of the association between higher infant death rates and adult coronary artery disease in contemporary peers who survived infancy [23] and between infant birth weights and insulin resistance [10] led Barker and colleagues to develop the “thrifty phenotype” hypothesis. That is, the prenatal environment has limited nutritional resources and would lead to metabolic changes, such as insulin resistance, enhanced energy storage, and decreased nephron number, to enhance postnatal success in an anticipated energy-limited environment. However, the infant encounters an imbalance that occurs between the prenatal and postnatal environment, with sufficient or even excess caloric exposure, leading to adverse consequences. This is described as a “programmed” effect that results from a permanent or long-term change in structure or function through metabolic imprinting and/or epigenetic changes, acting at critical period of early life. This concept was incorporated into developmental plasticity, defined as variations in developmental pathways that are triggered by environmental events during sensitive periods in development [24], which others call critical windows of sensitivity [25] (or windows of susceptibility). These windows typically occur during periods of rapid growth [25]. Several different models have been proposed to explain these findings. The theoretical frameworks include, among others, thrifty genotype [26] as well as thrifty phenotype [10]; developmental plasticity [24]; ecobiodevelopmental framework [27]; life history theory [28]; adaptive calibration model; and developmental origins of adult disease [29]. A similar perspective is the predictive adaptive response, which is a response to an environmental factor that may not be of immediate benefit but made in expectation of a future environment [30]; environment could include not only in utero factors, but also postnatal psychosocial, nutritional, or chemical exposures. These responses carry costs, as suggested by life history theory [28,31]; increased allocation of resources to brain growth or energy storage would reduce resources for other traits, such as tissue repair processes. These adaptations are considered the basis of the adverse consequences of fetal undernutrition and

maternal overnutrition, leading to the fetal origins of adult disease [32]. As discussed later, the adaptations in structure and function are long-term or permanent, and there is increasing evidence that epigenetic mechanisms may be responsible, prompting some to suggest that, rather than a thrifty genotype [26] or thrifty phenotype [10], the underlying mechanism is the thrifty epigenotype, incorporating both hypotheses through proposing epigenetic variations to enhance energy storage and utilization [33]. These hypotheses resulted in a renewed interest in exposures that occur at periods of increased susceptibility, such as during fetal development and puberty. For example, Barker noted the relationship between small-for-gestational-age status and greater prevalence of adult hypertension [4]. Brenner suggested that small-for-gestational-age status may be associated with decreased nephron number [34] and subsequent risk of hypertension. Zandi-Nejad and colleagues reviewed the role of fetal programming on adult hypertension and kidney disease and suggested several explanations, including epigenetic changes, increased apoptosis in the fetal kidney, increased exposure to fetal glucocorticoids, and alterations in the renin-angiotensin system [35].

Pubertal Milestones and Relative Timing of Puberty

Puberty represents an important developmental window of vulnerability to environmental exposures. Puberty is a time of rapid and profound change, including (re)activation of the hypothalamic-pituitary-gonadal and hypothalamic-pituitary-adrenal axes, an acceleration in height velocity and achievement of the pubertal peak height velocity, changes in body composition, the development of secondary sexual characteristics, and the achievement of fertility. The temporal relationships between these events are shown in Figure 1, and compared with timing of breast development. During puberty, there is rapid expansion and differentiation of breast stem cells, as discussed later, which occurs contemporaneously with reactivation of the hypothalamic-pituitary-ovarian axis, the onset of the pubertal growth spurt, and the time of maximal accrual of bone mineral content. The temporal relationships between these factors may suggest shared or underlying biologic mechanisms.

The timing of puberty may serve as a sensitive indicator of environmental change [36]. There is a 4-year variability in onset of puberty in girls [37]. It is estimated that 61% to 75% of the variation in age at menarche, which is correlated to onset of puberty, is attributable to direct or additive genetic effects [38,39]. Recent reviews reported that there are 42 loci associated with timing of puberty but noted that these loci make a small contribution (3.6%–6.1%) to the variability of age at onset [40,41]. Greater BMI during childhood is associated with earlier age at menarche [42,43]; this association may be related to greater levels of leptin reflecting sufficient energy stores [44] or other mechanisms associated with visceral adiposity [45,46]. Parent et al. reviewed other factors that could impact variability in timing of puberty: they include genetic factors and intrauterine environment, as noted previously; nutritional intake; climatic exposures; light-dark cycle; and exposure to endocrine-disrupting chemicals [47].

Psychosocial Factors and Puberty

In addition to metabolic and biologic exposures, studies have linked timing of puberty in girls to adversity in the psychosocial realm. Consistent with evolutionary life history theory, Belsky and colleagues [48] posited that when girls encountered

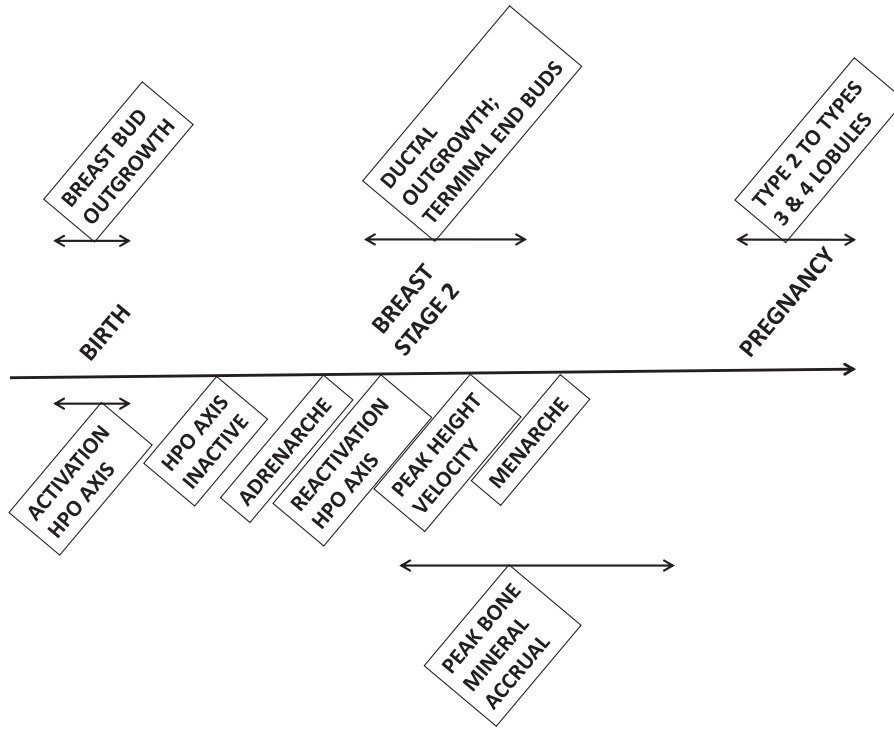


Figure 1. Pubertal milestones and breast development.

conditions that were not favorable for survival (i.e., environmental stressors), it was generally adaptive for them to become reproductively mature at earlier ages [48]. Empirical evidence has confirmed that childhood adversity accelerates girls' pubertal development [49]. In countries that have adequate nutrition, such as the United States, lower socioeconomic status has been associated with earlier menarche, although effects may vary depending on race/ethnicity [50]. In addition, harsh-conflictual family dynamics and poor parent-child attachment predict earlier maturation, whereas warm and supportive family conditions forecast later puberty among girls [51–54]. The absence of a biological father also has been associated with earlier pubertal timing, such that girls with no father in the home prepubertally are about twice as likely to experience menarche earlier than age 12 years than those with a father present [52,54–58]. Studies of stepfathers have yielded inconsistent findings, and there is no evidence to suggest that a mother's absence influences puberty; however, the presence of siblings may play a role in delaying menarche [55,59].

The role that prepubertal BMI may play in mediating associations between adverse family factors and girls' pubertal development is somewhat unclear. Some studies suggest that the influence of father absence on girls' pubertal development is mediated by BMI [60], whereas other studies do not note BMI as a mediator [56,61]. Future research is needed to further explore whether BMI or other measures of body composition (e.g., visceral adiposity) may help explain associations between adverse family factors and girls' pubertal timing.

Pubertal Events and Breast Cancer

Recently, attention has been turned toward the associations between early life events, pubertal changes, and risk for breast

cancer in adulthood. Although exposures across the life span have been linked to breast cancer risk [2], the mechanisms underlying the relationship remain unclear. During puberty, mammary growth occurs through exponential cellular proliferation and differentiation, suggesting a stem-like cell with regenerative capacity [62], and the mammary gland undergoes extensive changes. Primary ducts grow and divide with formation of terminal end buds, which further divide into smaller alveolar buds and form the lobule type 1 unit. There is additional growth and differentiation into lobules 2 and 3 throughout puberty and into adulthood (Figure 1). Of note, breast epithelium exhibits maximal proliferative activity during the luteal phase of the menstrual cycle, and the highest level of cell proliferation is observed in undifferentiated lobule type 1 [63]. Full differentiation into lobule type 4 occurs as a result of pregnancy, with permanent alterations in gene expression pattern. These pregnancy-associated changes have been hypothesized to result in cells that are more refractory to environmental exposures [64,65], unlike the earlier progenitor cells that are believed to be the cellular target for potential carcinogens and is proposed as the mechanism underlying decreased risk for breast cancer with earlier age at first full-term pregnancy [66]. For example, local girls 19 years or younger when the Nagasaki and Hiroshima atom bombs were dropped were more likely than local adults to develop breast cancer [67], suggesting an increased susceptibility for younger women to the effects of radiation.

There are several epidemiologic associations between pubertal events and risk of breast cancer, including age of menarche, growth factors (height and height velocity), and bone mineral density. Epidemiologic studies support up to 30% increased risk with younger age at menarche [2,68–72]. A pooled analysis reported that for each year that age of menarche was delayed, the risk of premenopausal breast cancer was reduced by

9%, and risk of postmenopausal breast cancer was reduced by 4% [68]. Menarche is one of the most well-established risk factors for breast cancer, in part because the age at which menarche occurred can be recalled years later [73]. Young age at onset of menarche is associated with young age at onset of breast development and with young age during the pubertal growth spurt. Young age during the pubertal growth spurt is associated with greater growth velocity [74]. Of note, obese and tall children have greater levels of IGF-1 in response to growth hormone than do short and normal-weight children [75], and IGF-1 may mediate the relationship between menarche and breast cancer. A recent study noted that the age at menarche was associated with risk of breast cancer, but not when age at peak growth was included in the analysis: this study found that risk for breast cancer increased 11% for every 5-cm increase in adult height [76]. Similarly, if a woman reached her maximum height at or before age 12 years, her risk of breast cancer increased by 1.4 [77]. Several studies documented the relationship between greater bone mineral density and later development of breast cancer [78–82]. Of note, the majority of bone mineral content is deposited during the teenage years, peaking shortly after the age at peak height velocity [83].

With regard to the concept of “windows of susceptibility,” important factors may expand the window or lead to more intense exposures. For example, early maturation leads to longer duration of puberty and to a greater peak height velocity. That is, early age at onset of puberty is associated with longer interval between onset of puberty and menarche [84–86] and therefore longer time for completion of puberty [84], with an increased risk for perturbation during cell proliferation and differentiation. Similarly, early age at onset of puberty is associated with greater height velocity (and IGF-1 levels) [84,87]; and greater IGF-1 levels are associated with greater premenopausal breast density [88,89], another factor associated with risk of breast cancer. In addition, the risk of breast cancer (and several other cancers) increases with greater height [90], with a 1.17 increased risk for every 10 cm of adult height. As noted earlier, greater BMI is associated with earlier maturation in girls, and earlier maturation is associated with higher BMI and increased risk of obesity. An analysis from the Bogalusa Heart Study found that greater childhood BMI was associated with earlier pubertal onset, and earlier puberty with greater BMI as an adult, but the relationship suggested that childhood BMI was the major factor [91]. A recent review suggests how IGF-1 might impact risk of cancer [89]: the action of IGF-1 promotes tumor growth and mitosis, inhibits apoptosis, and induces endothelial growth factor. Multiple reviews discuss the association of obesity and several different cancers [92], and as well as the underlying mechanisms for this association, which include pro-inflammatory cytokines [93].

It is important to consider a life course approach in the care of the adolescent. There is limited evidence, however, for interventions to decrease risk of later breast cancer in children and adolescents. Multiple studies have documented an increased risk of breast cancer with exposure to ionizing radiation during childhood and adolescence, both from survivors of nuclear bombs [94], as well as lower dose exposures [95], including serial radiographs for scoliosis, especially with a family history of breast cancer [96]. These studies would suggest that minimizing children and adolescents to ionizing radiation exposure would be beneficial. Another potential exposure is alcohol; in a review of dietary factors and breast cancer, alcohol was the only consistent factor associated with increased risk [97], perhaps mediated

through the association of alcohol with increased breast density. Although the literature is somewhat inconsistent, soy intake may be beneficial, with some studies citing intake during childhood [98] or during adulthood [99]. Physical activity levels may also be protective, and a case-control study noted that physical activity at ages 14 to 20 years decreased risk of breast cancer [100]. The relationship between hormonal contraceptives and breast cancer is controversial, although risk in younger users with BRCA1 and BRCA2 mutations may be increased modestly [101].

This article provides a brief review of a rapidly evolving field of inquiry, the developmental basis of adult disease, with an emphasis on the concepts of developmental plasticity and windows of susceptibility. We have focused on one adult disease, breast cancer, to discuss how changes during puberty may be particularly important for later disease. This is especially relevant for health providers of adolescents, who are familiar with a life course model of health, but may be unaware of studies from early life research or on adult outcomes. Early life factors may impact pubertal changes and predisposition to specific adult morbidities and mortality. The long-term changes may be mediated through epigenetic changes, as well as or resulting in, structural and functional changes to organs and body systems, and are implemented by the developing organism to enhance survival. The long-term sequela of these responses to early exposures may apply to several other adult morbidities and addressing these exposures represent an important challenge for contemporary medicine.

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