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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.

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 disorders using 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. Zendi-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