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Early Life Exposures and Adult Cancer Risk

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Very little is known about the influence of early life exposures on adult cancer risk. The purpose of this narrative review was to summarize the epidemiologic evidence relating early life tobacco use, obesity, diet, and physical activity to adult cancer risk; describe relevant theoretical frameworks and methodological strategies for studying early life exposures; and discuss policies and research initiatives focused on early life. Our findings suggest that in utero exposures may indirectly influence cancer risk by modifying biological pathways associated with carcinogenesis; however, more research is needed to firmly establish these associations. Initiation of exposures during childhood and adolescence may impact cancer risk by increasing duration and lifetime exposure to carcinogens and/or by acting during critical developmental periods. To expand the evidence base, we encourage the use of life course frameworks, causal inference methods such as Mendelian randomization, and statistical approaches such as group-based trajectory modeling in future studies. Further, we emphasize the need for objective exposure biomarkers and valid surrogate endpoints to reduce misclassification. With the exception of tobacco use, there is insufficient evidence to support the development of new cancer prevention policies; however, we highlight existing policies that may reduce the burden of these modifiable risk factors in early life.

adult cancer risk; diet; early life exposures; methodological strategies; obesity; physical activity; policies and research initiatives; tobacco use

Abbreviation: ETS, environmental tobacco smoke.

INTRODUCTION

Exposure to established modifiable cancer risk factors such as tobacco use, obesity, diet, physical activity, infectious agents (refer to the review by Vedham et al. (1)), and ultraviolet radiation (refer to the review by Balk et al. (2)) can begin in early life (Table 1). Currently, there are major gaps in our understanding of how these exposures in early life, either alone or in combination with other environmental and genetic factors, influence subsequent cancer risk (3, 4). Such gaps are due, in part, to the significant methodological challenges to studying early life exposures, such as the limited validity and reliability of long-term exposure measurements and long induction periods between early life exposures and cancer outcomes in adulthood (3). Thus, to date, epidemiologic research has focused primarily on older adult populations; very little is known about the etiological relevance of exposure to modifiable risk factors in other stages of the life course, and whether temporal factors, such as stage of development and/or duration of exposure, modify the influence of early life exposures on adult cancer risk (5). Epidemiologic studies designed to address these significant knowledge gaps could provide important insights into etiology and help to identify critical points for targeting interventions that may achieve the greatest benefit for cancer prevention (3, 4).

The purpose of this narrative review is 3-fold. First, we synthesize the current state of epidemiologic evidence linking early life exposures and adult cancer risk. A systematic evaluation of all cancer risk factors is beyond the scope of this narrative review; therefore, we limit our focus to the most common and modifiable cancer risk factors, namely, tobacco use, obesity, diet, and physical activity, which account for approximately 50% of all cancers (Table 1) (4, 6, 7). Next, to facilitate the epidemiologic study of early life exposures and adult cancer risk, we describe theoretical frameworks and methodological strategies that may address some of the current challenges associated with studying early life exposures. Finally, based on the summary of evidence presented, we identify potential policies and research initiatives that address early life exposures.

Table 1. Prevalence of the Most Common Modifiable Risk Factors for Cancer in Adulthood and Early Life in the United States[a]

Risk Factor	Cancers Caused by Risk Factor, %[a]	Cancer Sites[b]	Examples of Risk Factor Prevalence		
			Adulthood	Childhood and Adolescence	In Utero
Tobacco	33	Lung, mouth, larynx, pharynx, esophagus, stomach, colon/rectum, pancreas, kidney, bladder, cervix, ovary, myeloid leukemia	18% use tobacco.[c]	40% of children are exposed to ETS in the home[d]; 7.4% in middle school and 25.3% of high school students use tobacco.[f]	10.7% of women smoke during pregnancy.[e]
Overweight and obesity	20	Breast, endometrium, colon/rectum, kidney, pancreas, esophagus, gallbladder, ovary, thyroid, possibly prostate	66% are overweight or obese.[g]	22.8%–34.5% are overweight or obese.[g]	51.3% of reproductive age women are overweight or obese.[g]
Diet	5	Breast, colon/rectum, possibly pancreas	67.1%–95.2% do not meet recommendations for fruit/vegetable intake[h]; 80.2%–91.5% exceed recommendations for sugar/fat intake.[h]	39.6%–98.4% do not meet recommendations for fruit/vegetable intake[h]; 71.6%–99.9% exceed recommendations for sugar/fat intake.[h]	86.0%–91.5% of reproductive age women exceed recommendations for sugar/fat intake.[h] 74.8% of reproductive age women do not meet recommendations for fruit/vegetable intake.[h]
Physical inactivity[h,i]	5	Breast, endometrium, colon	50.8% do not meet recommendations for physical activity.[i]	58.0%–92.0% do not meet recommendations for daily physical activity.[j]	48.4% of reproductive age women do not meet recommendations for physical activity.

Abbreviation: ETS, environmental tobacco smoke.
[a] Adapted from Colditz et al. (4).
[b] Source: American Cancer Society (7).
[c] Source: US Department of Health and Human Services (8).
[d] Source: Homa et al. (281).
[e] Source: Tong et al. (280).
[f] Source: Singh et al. (252).
[g] Source: Ogden et al. (33).
[h] Source: National Cancer Institute (282).
[i] Source: Centers for Disease Control and Prevention (283).
[j] Source: National Physical Activity Plan Alliance (284).

METHODS

For this narrative review, we focused on peer-reviewed, epidemiologic studies relating tobacco use, obesity, diet, and physical activity during periods of early life, namely, in utero, childhood, and adolescence (<21 years), to adult cancer risk. We used a life-course epidemiology framework to guide our literature search, focusing on evidence for associations of these risk factors with cancer and/or well-established cancer risk factors (e.g., obesity in adulthood). We conducted MEDLINE searches for English-language epidemiologic studies published in the peer-reviewed literature through July 2016, including combinations of the following terms: "pregnancy," "in utero," "gestational," "prenatal," "birth weight," "fetal growth," "childhood," "adolescence," "youth," "early-life," "offspring," "tobacco," "smoking," "body size," "adiposity," "weight gain," "obesity," "diet," "nutrition," "breastfeeding," "physical activity," "exercise," "puberty," "menarche," "cancer," and "carcinogenesis." We did not restrict by country of origin. We identified additional relevant articles in the References section of articles identified by our search process. We prioritized systematic reviews, meta-analyses, and population-based, prospective cohort studies. We also included government reports, including the Surgeon General's reports on tobacco use (8, 9). Theoretical frameworks and methodological strategies described focus on issues addressed during workshops held by the National Cancer Institute and the Centers for Disease Control and Prevention on this topic (3, 10), as well as methods from the causal inference literature (11, 12). On the basis of our review of the literature, we identified current research initiatives and US-based policies and/or programs that address the early life exposures.

EPIDEMIOLOGIC EVIDENCE LINKING EARLY LIFE EXPOSURES TO ADULT CANCER RISK

Tobacco

Over 90% of adult smokers try their first cigarette before 18 years of age, making adolescence and young adulthood a

critical period for lung cancer risk (8). Young age of smoking initiation increases lung cancer risk by increasing cumulative exposure to tobacco smoke and may also represent a critical developmental period for enhanced lung cancer susceptibility (8, 13). With respect to other cancers, the evidence is less clear; cigarette smoking in young adulthood likely influences the early stages of colorectal carcinogenesis, supported by the consistent association of smoking and adenomas (8). For breast cancer, the timing of smoking relative to critical periods of breast development (e.g., pregnancy) may be important (8, 14), although the current evidence is insufficient to support this hypothesis (8).

Childhood tobacco smoke exposure occurs primarily through environmental tobacco smoke (ETS). With respect to childhood ETS exposure and lung cancer risk, findings from the meta-analysis of 24 studies included in the latest Surgeon General's report on ETS published in 2006 suggested some heterogeneity across studies but an overall null association (9). More recently, findings from 2 case-control studies with independent validation suggested a positive association of childhood ETS exposure with lung cancer risk, with potential effect modification by genetic variants involved in lung physiology and immunity (15, 16). More research is needed to determine whether gene-environment interactions can help to clarify the heterogeneity observed within and across studies (17).

Exposure to tobacco smoke in utero occurs indirectly from maternal smoking and/or maternal ETS exposure. Although some studies suggest a modest association between in utero exposure to paternal ETS and childhood leukemia (9, 18–22), current evidence does not support an association with adult cancer risk (9, 15, 16, 23, 24). Experimental and epidemiologic evidence suggests potential associations of maternal smoking with risk of obesity and metabolic syndrome in child offspring, which may increase their risk for certain types of cancer later in life. Indeed, findings from a recent systematic review and meta-analysis of 39 epidemiologic studies suggest an association of maternal smoking with childhood obesity, independent of important confounders such as socioeconomic status, maternal age, and body mass index (25). Prenatal ETS exposure has also been associated with aberrant fetal hormonal and growth factor signaling and early onset puberty, which could have implications for offspring risk of hormone-associated cancers later in life (26–28). Two recent systematic reviews and meta-analyses reported an association of prenatal ETS exposure with early onset puberty in both males and females (29, 30); however, according to a meta-analysis of 11 case-control studies, prenatal ETS exposure was not associated with risk of testicular cancer (30). Importantly, a majority of the studies included in the systematic reviews and meta-analyses ascertained prenatal ETS exposure through maternal self-report, which could be subject to recall bias and/or misclassification (31, 32).

In summary, the association between adolescent exposure to tobacco smoke and lung cancer risk is well-established. More research is needed to determine the independent effects of childhood and in utero ETS exposure on risk of lung and other cancers in adulthood. Incorporation of gene-environment interaction analyses may help to clarify the heterogeneity observed within and across studies of lung cancer (17).

Overweight and obesity

Nearly one-third of children and adolescents are overweight or obese (33), putting them at greater risk for chronic diseases, including certain cancers, later in life (34, 35). Childhood obesity and adolescent obesity have been associated with decreased risk of premenopausal breast cancer and benign breast disease, irrespective of adult body mass index (36, 37). Although the health risks associated with obesity far outweigh any potential benefit with respect to premenopausal breast cancer, this association provides important clues about how adiposity during a critical window of breast development (e.g., puberty) can influence subsequent cancer risk (36). With respect to other obesity-related cancers, US prospective cohort and population-based case-control studies have consistently demonstrated an association of weight gain since the age of 18 years with risk of endometrial cancer (38–44). Some of these studies also reported a positive association of obesity in adolescence with endometrial cancer risk, mediated by obesity in adulthood (38, 41, 45). The evidence for colorectal cancer is also fairly consistent, with most studies supporting an association of obesity in adolescence and weight gain from early to later adulthood with increased risk of colorectal cancer, although a majority were restricted to men only (46–49). In studies that included both sexes, 1 reported a stronger association among women compared with men (50), while others reported a stronger association among men (51, 52). In a large cohort study of older women assessing body mass index at multiple time periods, only weight gain since age 18 years and adult body mass index were positively associated with colorectal cancer risk (53). Data from prospective studies for other cancer types remain sparse, but they suggest potential associations between early life obesity and risk of esophageal cancer (54, 55), pancreatic cancer (56), and multiple myeloma (57). A pooled analysis of 20 cohort studies found that elevated body mass index at ages 18–21 years was a more significant predictor of pancreatic cancer mortality than body mass index gain in adulthood (58). In support of some of these findings, a series of population-based studies of school health records from over 140,000 children linked to Danish Cancer Registry data has demonstrated a positive association of childhood body mass index with risk of endometrial, esophageal, liver, and thyroid cancer in adulthood (59–62) but not with prostate cancer (63, 64). Of note, these studies were unable to adjust for adult body mass index.

Current evidence does not support an association between in utero exposure to maternal obesity and/or gestational weight gain with adult cancer risk. However, maternal obesity, like gestational diabetes (65–67), has been consistently associated with increased infant and early childhood growth (68–77). Experimental evidence suggests that this association may be mediated by higher levels of maternal glucose and fatty acids crossing the placenta, leading to increased fetal insulin production and adipose tissue accumulation (66, 78, 79), as well as potential deregulation of hypothalamic and neuroendocrine pathways responsible for long-term energy balance (80–82). This hypothesis is supported

by evidence from early studies of women who underwent bariatric surgery between pregnancies, reporting a decreased prevalence of overweight and obesity and lower blood glucose, insulin, lipid, and triglyceride levels in offspring born after surgery compared with their siblings born prior to surgery (76, 77). Data from recent meta-analyses and additional prospective studies suggest that excess gestational weight gain may also influence early childhood adiposity (83–86), although the evidence is less consistent in studies among older children (87–91). Several epidemiologic studies have evaluated the association of birth weight with adult cancer risk. Recent systematic reviews and meta-analyses suggest a positive dose-response relationship between birth weight and breast cancer risk (92), a modest positive association of birth weight with total and aggressive/lethal prostate cancer (93), and an inverse relationship between birth weight and testicular cancer (94). Some prospective studies have also shown a positive association between birth weight and risk of colon cancer and adenomas (95–97), while others have demonstrated a J-shaped (98) or inverse (99) relationship between birth weight and colorectal cancer risk. These discrepancies could be attributed to use of self-reported birth weight in some studies (96–98) and/or lack of adjustment for potential confounders in adulthood (95, 98, 99).

In summary, childhood obesity and adolescent obesity have been associated with a decreased risk of premenopausal breast cancer, as well as a suggestive increased risk of several other cancers, including endometrial, colorectal, and pancreatic cancers. More work is needed to better clarify the etiologically relevant time windows for early life obesity and adult cancer risk. There is limited evidence that exposure to maternal obesity and/or gestational weight gain in utero directly influences adult cancer risk, but there is strong evidence that these exposures are associated with early life and potentially adult adiposity, thereby indirectly increasing risk for many cancers.

Diet

Childhood and adolescent dietary exposures have been extensively studied in relation to breast cancer risk (100, 101). Studies of Japanese migrants were some of the first to indicate an association of childhood exposure to a "Westernized" diet with adult breast cancer risk, providing preliminary support for a role for early life dietary exposures in breast carcinogenesis (102). A number of studies conducted among Asian and Asian-American women have reported a protective effect of childhood and adolescent soy intake against breast cancer risk, with stronger evidence for premenopausal breast cancer (103–107). In the Nurses' Health Study II, adolescent intakes of fiber, vegetables, and nuts were associated with reduced risk of premenopausal breast cancer (108, 109) and benign breast disease (110, 111), while adolescent intakes of fat and red meat have been associated with increased breast density and premenopausal breast cancer (112–114). These findings have been replicated in some (115–120), but not all (121, 122), studies. Certain high-fat foods have been associated with increased estrogen production and early menarche, a marker of prolonged estrogen exposure, which could have important implications for breast and other hormone-related cancers (123–126). In a randomized trial designed to reduce fat intake in children, females in the intervention arm had reduced estradiol and progesterone concentrations at 5 years of follow-up (123); however, these associations did not persist into young adulthood (124). Two recent prospective studies of young girls reported an association of caffeinated beverage consumption with early menarche; however, findings were inconsistent in regard to sugar-sweetened and artificially sweetened beverage consumption (127, 128).

With respect to other cancers, findings from the Nurses' Health Study II have reported associations between adolescent fish and poultry consumption (vs. red meat) and consumption of fruits, vegetables, and fish, with reduced risk of colorectal and rectal adenomas, respectively (129, 130). In the Boyd Orr cohort, childhood dairy intake was associated with colorectal cancer risk in adulthood, irrespective of meat, fruit and vegetable intake, and socioeconomic status (131). In the National Institutes of Health (NIH)-AARP Diet and Health Study, adolescent intakes of vegetables and vitamin A were associated with decreased colorectal cancer risk, independent of adult diet, whereas the protective effect for some nutrients, like calcium, was strongest when consumed in both adolescence and adulthood (132). In this same study, both adolescent and adult consumption of red and processed meat was associated with increased colorectal cancer risk, suggesting a cumulative effect (132). In a separate study from the same cohort, adolescent intake of foods rich in iodine was associated with thyroid cancer risk, whereas diet during midlife had no effect (133).

Although the literature does not support a direct relationship between in utero dietary exposures and adult cancer risk, there is a large body of research supporting a direct relationship between certain maternal dietary exposures (e.g., folic acid and long-chain fatty acids) and pre-and postnatal growth and development (134–136). Studies of prenatal famine exposure during the Dutch Hunger Winter following World War II were some of the first to demonstrate long-term effects of caloric restriction on offspring obesity and chronic disease risk (137, 138). Maternal overnutrition, particularly high-fat intake, has also been associated with offspring obesity risk in several prospective studies (139–142), potentially mediated through gestational diabetes and/or increased fetal exposure to fatty acids (143, 144). Some studies of specific maternal dietary patterns (140, 145–149), but not all (150–153), have reported associations with offspring growth and adiposity. To avoid potential misclassification associated with assessment of recalled dietary and nutrient exposures, some studies have explored the relationship between measures of overall maternal diet quality in relation to offspring growth and obesity risk (142, 154–156). For example, in a recent prospective study of adherence to the 2010 Dietary Guidelines for Americans, Shapiro et al. (156) found that nonadherence was related to increased neonatal fat mass, likely driven by total and saturated fat intake. In addition to maternal diet, numerous long-term beneficial effects of breastfeeding have been documented for both the mother and child, including decreased risk of offspring overweight and diabetes and of diabetes and breast and ovarian cancers in mothers (157–161).

In summary, childhood and adolescent diets have been most thoroughly studied with respect to breast and colorectal cancers; diets that are higher in fruits and vegetables, and

lower in red meat and fat, appear to be associated with a lower risk of these cancers. More work is needed to characterize the influence of childhood and adolescent diets on other adult cancers. There is no evidence that exposure to specific maternal dietary factors in utero directly influences adult cancer risk, but there is evidence that maternal diet is associated with early life growth and potentially later-life adiposity, thereby indirectly increasing risk for many cancers.

Physical activity

As with diet, childhood and adolescent physical activities have been most thoroughly studied with respect to breast cancer. In the Nurses' Health Study II, adolescent and lifetime physical activities were associated with reduced risk of premenopausal breast cancer (162, 163), with 1 study suggesting a stronger effect for women who had a long interval (<20 years) between menarche and first pregnancy (164). Despite these findings, most studies, including those conducted within the NIH-AARP and Women's Health Initiative cohorts, have not found an association of early life physical activity with reduced breast cancer risk (165–169). With respect to other cancers, vigorous physical activity during adolescence has been linked to reduced risk of Hodgkin lymphoma in women (170) and renal cell cancer (171–173). Some, but not all, studies have found an association between childhood and adolescent physical activity and reduced endometrial cancer risk (174–176).

Although the literature does not support an association of maternal physical activity with offspring cancer risk, the protective effects of exercise during pregnancy against excessive gestational weight gain and gestational diabetes are well-established (177–183), which could potentially mitigate the risk of offspring obesity (182, 184–190). The direct effects of maternal physical activity on offspring size and growth are unclear; some systematic reviews and meta-analyses have reported a modest association with lower birth weight and reduced risk of delivering a large-for-gestational-age infant (191–193), but not all (177, 194). In 1 small, community-based randomized trial, moderate-intensity exercise in late pregnancy was associated with lower birth weight and reduced fetal insulin-like growth factor I/II levels in cord blood (195).

In summary, there is inconsistent evidence that physical activity in adolescence may be protective against breast cancer. More work is needed to better characterize the influence of physical activity in adolescence on other adult cancers. Childhood physical activity has largely been unstudied with respect to adult cancer risk. There is no evidence that exposure to maternal physical activity in utero directly influences adult cancer risk, but there is evidence that maternal physical activity can reduce excess gestational weight gain, thereby indirectly decreasing risk for childhood adiposity and potentially adult cancer risk.

THEORETICAL FRAMEWORKS AND METHODOLOGICAL STRATEGIES FOR STUDYING EARLY LIFE

Epidemiologic studies of early life exposures and cancer risk require unique design and analytical considerations. The long time interval presents a challenge for reliable and accurate exposure measurement and increases the possibility of misclassification and confounding by later-life exposures (196). Here we describe theoretical frameworks and methodological strategies that may be particularly useful for studying early life exposures and adult cancer risk.

Multistage models of carcinogenesis

The 2-stage clonal expansion model assumes 3 phases of carcinogenesis: 1) the acquisition by a susceptible stem cell of 1 or more genetic or epigenetic changes ("initiation"); 2) clonal expansion of initiated cells ("promotion"); and 3) malignant transformation of 1 of the initiated clones via additional genetic and/or epigenetic changes (197). Early life exposures, such as tobacco smoke and diet, may affect different phases of this multistage process and, in some cases, may exert differential effects (198, 199). The widely used Cox proportional hazards model offers flexibility in assessing temporal aspects of an exposure-outcome relationship; if nonproportionality is suspected, time-dependent variables can be modeled with an interaction term for the covariate of interest and time (200–202). An alternative, fully parametric approach is the mathematical 2-stage clonal expansion model, which is biologically based and can incorporate complex temporal exposure patterns, including age at initiation/cessation and intensity into the analyses (for detailed methods, refer to Moolgavkar and Luebeck (199)). Rather than a hazard ratio, this approach uses likelihood-based methods to estimate individual hazard functions for specific exposure histories, which can be converted into relative risks by taking the ratio of the estimated hazard functions. This model has been used to show that smoking affects mainly the promotion of lung carcinogenesis (203), to estimate optimal colorectal cancer screening schedules (204, 205), and to clarify the dual effects of folate supplementation on colorectal carcinogenesis (206, 207).

Life-course epidemiology models

The life-course approach to chronic disease epidemiology, proposed by Ben-Shlomo and Kuh (5), provides a framework for developing hypotheses about the different pathways through which early life exposures may influence cancer risk (Figure 1). For example, during "critical" or "sensitive" developmental periods (e.g., in utero and puberty), exposures may modify processes related to growth and development by inducing permanent changes in tissue differentiation, metabolism, and gene expression that directly or indirectly influence cancer risk (5, 208). Retrospective ascertainment of early life exposure data is particularly prone to both nondifferential and differential misclassification due to long recall times and/or recall bias, which can attenuate effect estimates and result in spurious associations, respectively (3, 209). Moreover, including misclassified early life exposures in a multivariable model with later life exposures, presumably measured with greater precision and accuracy, can distort relative risk estimates, particularly if those exposures are strongly correlated (209). The identification of objective and reliable exposure biomarkers may

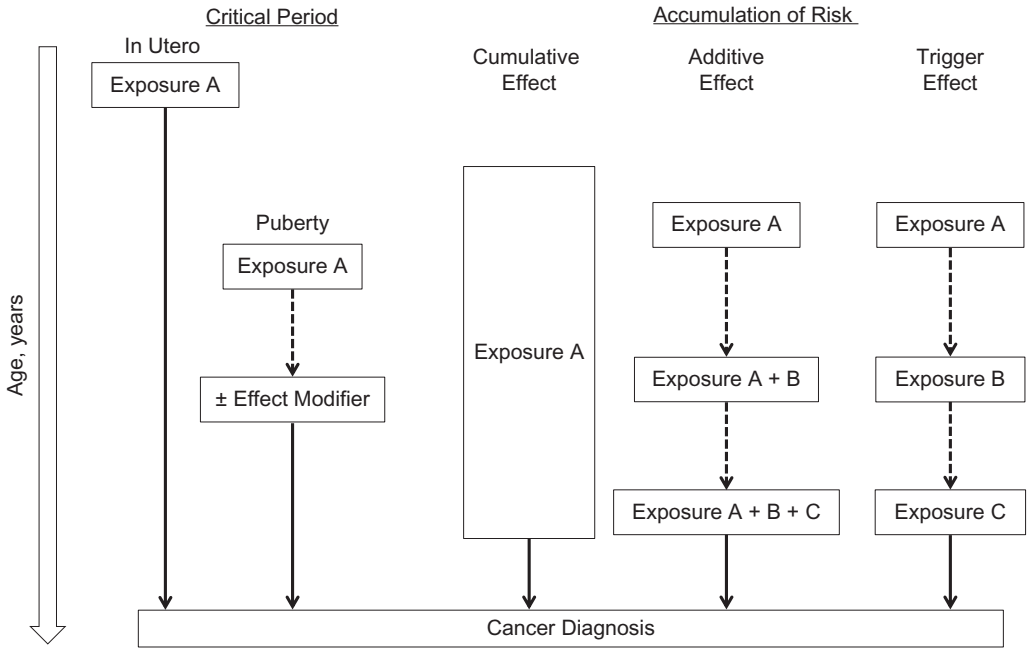

Figure 1. Life-course epidemiology frameworks. The "critical period model" depicts how early life exposures can act during a critical period of development (e.g., in utero or puberty) and have lasting effects on future cancer risk, with or without the presence of effect modifiers later in life. In contrast, the "accumulation of risk models" depict how early life exposures can contribute to future cancer risk by increasing the duration of lifetime exposure ("cumulative effect"), leading to other exposures later in life such that each exposure increases cancer risk in a cumulative fashion ("additive effect," exposures A + B + C) or indirectly by increasing the likelihood of a causal exposure ("trigger effect," exposure C) later in life.

address some of the challenges related to early life exposure measurement, although very few have been identified (3). Epigenetic modifications, such as DNA methylation, are critical for regulating cellular processes during development and responses to endogenous and exogenous exposures that are maintained over time. There has been growing interest in evaluating DNA methylation changes as biomarkers of early life exposures (refer to the report by Ladd-Acosta (210)). For example, several studies have reported an association of maternal cigarette smoking with DNA methylation changes in cord blood (211–217), with some evidence suggesting postnatal stability of these changes in children (212, 218–222) and adults (223–226). Although promising, large gaps in our understanding of the long-term stability, tissue specificity, and functional relevance of these DNA methylation changes limit their current utility as long-term biomarkers (227). Initiatives such the Roadmap Epigenomics Mapping Consortium may address some of these fundamental questions (228). In addition to understanding the biology of DNA methylation, researchers continue to develop epidemiologic methods related to quality control assessment, site-specific versus region-based analyses, and the most appropriate statistical models for detecting associations (227). Use of functional annotation tools, such as the University of California, Santa Cruz, Genome Browser (https://genome.ucsc.edu), may lead to hypotheses regarding the functional significance of DNA methylation changes to help inform some of these methods (227).

In addition to biomarkers of early life exposures, surrogate endpoints could potentially overcome some of the limitations associated with long-term exposure measurement (196). A surrogate endpoint can be defined as a measurable marker of preclinical carcinogenesis that lies on a causal pathway linking an exposure to cancer risk or, in some cases, is closely linked to a component of the causal pathway (229). Types of markers include histological changes, cellular processes (e.g., proliferation and apoptosis), molecular markers, infectious agents, cytokines, hormones, and prognostic factors (e.g., tumor recurrence) (229). Although the rapid advancement of high-throughput technologies has enhanced our ability to measure new markers, relatively few examples of valid surrogate endpoints exist in the cancer literature (e.g., colorectal adenoma, cervical intraepithelial neoplasia) (229). The presence of alternative causal pathways poses a major challenge to validating surrogate endpoints; if a potential surrogate is not a necessary component of the carcinogenic pathway, an estimate of its association with an exposure may not accurately reflect the association between the exposure and the true cancer endpoint (230). This is particularly problematic if an exposure influences an alternative pathway that offsets the effect of the exposure on the surrogate (229). To overcome some of these limitations, putative surrogates, ideally measured over multiple time points, should be integrated into studies with cancer outcomes so that they can be evaluated (229).

Early life exposures may also gradually accumulate over the life course such that their cumulative effect increases

cancer risk (5) (Figure 1); however, this is often difficult to measure in epidemiologic studies (3). The tobacco literature defines cumulative exposure as the product of smoking duration and intensity (i.e., "pack-years"); however, the term, pack-years, does not account for other temporal factors such as intensity and age at smoking initiation/cessation (231). Expanded models that include parameters for smoking duration and intensity are difficult to interpret as they necessarily incorporate pack-year associations when either 1 of those parameters is conditioned on (232). To address this issue, Lubin and Caporaso (233) developed a model that includes pack-years as the primary exposure and incorporates variables related to smoking intensity as effect modifiers, which enables estimation of cumulative exposure at varying intensities (e.g., smoking 2 packs/day for 40 years vs. 4 packs/day for 20 years). Vlaanderen et al. (234) refined this model to include time since quitting as an effect modifier and cubic splines for flexible modeling of smoking intensity. Together, these methods have informed lung cancer etiology and have helped to identify potential targets for intervention (231). Extending these approaches to other exposures may provide insight into whether the use of cumulative exposure alone, or in combination with other time- and intensity-related variables, is justified.

Exposures may also be linked over time as "chains of risk" with "additive" or "trigger" effects (5) (Figure 1). In the additive effect model, each subsequent exposure increases cancer risk. In the trigger effect model, only the most proximal ("final link in the chain") exposure is causal, and all other exposures indirectly influence cancer risk (5). Longitudinal studies with repeated measures provide an opportunity to assess temporal exposure patterns; however, traditional linear models (e.g., analysis of variance and growth curves) are limited by equal variance assumptions and balanced data requirements, and they are not equipped to model complex temporal patterns of exposure in relation to cancer risk (235). To overcome some of these limitations, finite mixture modeling approaches like growth mixture (236) and group-based trajectory modeling (237) have been developed to analyze populations composed of distinct exposure trajectories that are not easily distinguished by measured characteristics (for a review, refer to the article by Nagin and Odgers (235)). Both group-based trajectory and growth mixture models can be adapted to allow the probability of trajectory group membership to vary by fixed and/or time-varying covariates (235). By use of the growth mixture modeling approach, 2 or more growth curve models are established a priori to estimate population variability in developmental trajectories and interpreted in a similar way as a single growth curve model, with each representing a separate subpopulation following a different trajectory curve (235). On the other hand, group-based trajectory modeling approximates an unknown distribution of trajectories within the population. A useful feature of this approach is the ability to estimate the probabilities linking trajectory group memberships across different exposures (e.g., childhood diet and obesity in young adulthood) (235, 237). These methods have been applied in 2 recent prospective studies assessing trajectories of body shape in early life with adult cancer and cause-specific mortality (238, 239).

Additional approaches to strengthen causal inference

The use of negative controls may help to strengthen causal inference in studies of early life exposures, particularly if residual confounding is suspected (11, 12). A negative control is defined as an exposure that is unrelated to the outcome of interest or an outcome that is unlikely to be caused by the exposure of interest, but that shares similar sources of bias and confounding (12). Negative control associations can be compared with the main effect estimate to rule out confounding and strengthen causal inference (12). For example, paternal exposures can serve as negative controls for studies of maternal exposures and offspring health (240); if there is a direct intrauterine effect on offspring health, then the association should be much stronger for the maternal exposure compared with the paternal exposure (12, 240). Negative controls have been utilized in studies assessing the influence of maternal diet during pregnancy on offspring dietary behaviors (153) and associations of maternal obesity with cord blood DNA methylation levels (241).

Mendelian randomization is a special type of instrumental variable analysis that involves using genetic variants as proxies for exposures of interest (242, 243). This approach is attractive for studies of early life exposures because of the following: 1) genetic variants are randomly inherited and, thus, exposure status is not influenced by other confounding factors; 2) use of germline variants is not subject to bias due to reverse causation; and 3) a genetic variant may represent long-term, cumulative exposure (244). Mendelian randomization has been used in studies of maternal smoking, demonstrating an association of a variant in the *CHRNA5-A3-B4* gene cluster that is strongly associated with heavy smoking and the inability to give up smoking during pregnancy, with low birth weight (245). A recent study utilized this approach to calculate a genetic score derived from single-nucleotide polymorphisms associated with Tanner stage in adolescent boys, demonstrating that later pubertal development reduces the risk of aggressive prostate cancer (28). Importantly, Mendelian randomization is appropriate only if the genetic variant is strongly associated with the exposure of interest; a genetic variant that influences more than 1 phenotype (i.e., pleiotropic), particularly if it is associated with both the exposure and outcome of interest, can introduce bias (244). Furthermore, if the genetic variant is correlated with other genetic variants (i.e., linkage disequilibrium), spurious associations may arise (244). Careful study design and analytical techniques (246, 247) can minimize these issues.

POLICY AND PUBLIC HEALTH–RELATED INTERVENTIONS AND RESEARCH INITIATIVES

Despite the large body of evidence linking early life exposure to the risk factors presented in this narrative review to numerous adverse health outcomes in both youth and adulthood, more research is needed to firmly establish associations with adult cancer risk. With the exception of youth tobacco exposure, our findings do not signify the need for specialized cancer prevention interventions, but they do provide additional evidence to support the need for ongoing efforts to reduce the burden of these risk factors in early life

and to emphasize important gaps in the literature. Here, we provide examples of public health interventions and policies aimed at reducing early life exposure to these risk factors. We also provide examples of recent efforts to build the evidence base of the health consequences of early life risk factors via research initiatives.

Some of the most effective federal- and state-level policies and initiatives have been focused on reducing ETS exposure and tobacco use among youth, including taxation, comprehensive smoke-free laws, and mass-media campaigns (248–251). However, in recent years, the rate of decline has slowed, with approximately 7.4% of middle school and 25.3% of high school students reporting current use of any tobacco product in 2015 (252). Moreover, use of flavored and alternative tobacco products is on the rise, with electronic cigarettes being the most common (252). In light of these trends, the US Food and Drug Administration recently extended its regulatory authority to cover all tobacco products, including e-cigarettes. The new rule also restricts youth access to such products by preventing retailers from selling to youth under the age of 18 years and prohibiting the sale of tobacco products in vending machines (except in adult-only facilities) (253). Other public policy initiatives, such as legislation to prohibit smoking in motor vehicles, and the promotion of smoke-free homes through educational campaigns (254–256) have been enacted in only a few states, highlighting the need for improvement (257, 258). In 2015, the US Department of Housing and Urban Development proposed a smoking ban in multiunit housing, with the potential to impact over 750,000 children and adolescents, if enacted (254). Newer strategies focused on sales restrictions and harm reduction have also been proposed (254). For example, a federal bill that raises the minimum tobacco age to 21 years, which the Institute of Medicine reports could reduce youth smoking initiation by 25% nationwide, is currently under Congressional review (259).

National- and state-level policies targeting obesity-related behaviors in youth have been implemented primarily in schools, which play a critical role in shaping the health behaviors of children and adolescents (260). For example, as part of the 2010 Healthy, Hunger-Free Kids Act, the US Department of Agriculture implemented new "Smart Snacks in School" nutrition standards in 2014 for foods and beverages sold at school (261, 262). More research is needed to determine the impact of these policies on eating behaviors and the prevalence of overweight and obesity among youth (262, 263).

Interventions delivered in clinical settings can also play an important role in supporting healthy behaviors relevant to cancer prevention; however, for many interventions, there is limited evidence demonstrating their effectiveness in improving health behaviors (264). For example, preconception care interventions, such as tobacco cessation and obesity prevention, have the potential to improve the health of 2 generations (265, 266) and are strongly recommended by the American Congress of Obstetrics and Gynecologists and the Institute of Medicine (267, 268). Yet, despite these recommendations, evidence for the effectiveness of most preconception care services is lacking (266), and even those with a strong-evidence base, such as tobacco cessation interventions, are not widely implemented in routine practice (267, 269, 270). Federal coverage mandates for preconception services under the Affordable Care Act, such as tobacco-cessation counseling and pharmacotherapy for pregnant women on Medicaid (271), offer promising strategies to improve uptake, although data suggest that more work is needed to increase provider awareness of these benefits (271, 272). Because many of the modifiable risk factors covered in this narrative review tend to track with time, delivery of evidence-based preventive services to children and adolescents provides an opportunity to intervene early to reduce or modify the burden of established cancer risk factors in adulthood (260). The US Preventive Services Task Force issues guidelines for preventive service recommendations for children and adolescents; however, these recommendations are not integrated across domains, and some important topics, such as physical activity and dietary counseling, are not included because of insufficient evidence (273). Further, delivery of preventive care to adolescents is relatively low (260, 274). Recent changes in the US health-care system expanding coverage for preventive services without cost sharing offer opportunities to improve utilization of preventive care services among youth (275). Lack of the high-quality evidence required for the development of guidelines and recommendations underscores the need for more research to fill these important gaps.

Building the evidence base of the health consequences of early life risk factors may require innovative use of existing data from cohorts with relevant intermediate exposures (e.g., puberty), as well as prospective studies that are designed to capture cancer risk factors in early life. To this end, several funding opportunities have been established. For example, the National Institutes of Health recently launched a 7-year initiative called the "Environmental Influences on Child Health Outcomes" (ECHO) program to understand the effects of environmental exposures on child health and development, with obesity as 1 of 4 key outcomes (276). In addition, the National Cancer Institute has funding opportunities for studies evaluating the role of early life factors in carcinogenesis and whether markers associated with early life exposures can be measured and developed for use in cancer prevention strategies (277). To address the need for surrogate cancer endpoints, a "Pre-Cancer Genome Atlas" has been proposed to complement *The Cancer Genome Atlas* (278, 279). Collectively, these efforts have the potential to bolster our understanding of the role of early life exposures in adult cancer risk.

CONCLUSIONS

The purpose of this narrative review was to emphasize early life as an important, yet understudied period with respect to cancer research. Although there is consistent evidence linking certain early life exposures in adolescence to adult cancer risk (e.g., tobacco use and lung cancer), more research is needed for a majority of the exposures described in this narrative review. With respect to in utero and early childhood exposures, much of the evidence is indirect, suggesting potential associations through the modification of

biological and/or behavioral pathways that may influence the trajectory of cancer risk over the life course. Collectively, this dearth of evidence emphasizes significant gaps in our knowledge regarding the period of early life with respect to adult cancer risk. Conceptual models, such as the life-course framework, may help to sharpen biologically based hypotheses about relevant time periods for cancer etiology, while statistical approaches, such as group-based trajectory modeling, have the potential to reveal novel associations and/or hidden heterogeneities within prospectively collected data; they also may help to identify critical points for targeting primary prevention strategies. In addition, objective molecular markers, such as DNA methylation, have the potential to improve early life exposure assessment and to elucidate mechanisms linking early life exposures with adult cancer outcomes (210, 227). The modifiable cancer risk factors described in this narrative review are also risk factors for other chronic diseases. Although the current evidence does not indicate the need for specific cancer prevention interventions in early life, it does support the need for the public health interventions that encourage overall health and well-being in young people. Continued research on early life exposures has the potential to provide new insights into cancer etiology and to inform primary prevention strategies to reduce the prevalence of cancer risk factors in the early stages of life, a time when these strategies might achieve the greatest benefit (4).

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