Invited Commentary

Invited Commentary: Are Dietary Intakes and Other Exposures in Childhood and Adolescence Important for Adult Cancers?

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In this issue of the Journal, Nimptsch et al. (Am J Epidemiol. 2013;178(2):172–183) report significant associations between female adolescents’ poultry consumption in high school and subsequent reduced risk of colorectal adenomas in adulthood. Consumption of red meat or fish was not related to risk, but replacement with poultry reduced the risk of later adenomas. Most epidemiologic studies of adult diseases lack exposure data from the distant past. By focusing on a cancer precursor lesion and using a variety of methods to assess data quality, the investigators address concerns about the quality of distant recall. These findings add to the growing evidence that links childhood and adolescent lifestyle and environmental exposures with subsequent risk of cancers arising in adulthood. Highlights of the literature on this topic and methodological challenges are summarized. Future studies would benefit from incorporating measures of lifestyle, diet, environmental exposures, and other risk factors from early in life and from validation and other data quality checks of such measurements. Sources of historical data on children’s and adolescents’ exposures should be sought and evaluated in conjunction with subsequent exposures in relationship to adult-onset cancers.

adolescence; diet; distant past; life course; methods; recall

Most epidemiologic studies of adult cancers have evaluated exposures during adulthood, but relatively few have examined earlier time periods (1). Emerging evidence suggests that early life exposures, in conjunction with genetic makeup, may be etiologically important for adult cancers, but there is a dearth of prospectively collected information from these early time periods. Current evidence relies on adult recall of limited numbers of past exposures. Some consideration has been given to prenatal and early postnatal exposures (2, 3), but childhood and adolescent exposures have only recently received more attention (4–6).

Results from studies of radiation exposure across the life course have provided the strongest evidence that early life is an influential time period for later cancers. Adult-onset leukemias and cancers of the breast, thyroid, lung, and skin have been clearly associated with childhood or adolescent radiation from the atomic bombings in Japan (7). Childhood or adolescent radiation exposures were linked with a substantial increase of thyroid cancer among residents exposed to the Chernobyl, Ukraine, nuclear accident (8) and among those with thyroid exposure from diagnostic x-rays (9) or radiotherapy for pediatric cancer of other organs (10). Repeated fluoroscopic examinations (for monitoring of tuberculosis) or radiographic examinations (for monitoring the progression of scoliosis) in childhood and adolescence have been linked with excess risk of adult breast cancer (7). Peak adult breast cancer risks were linked with exposures in childhood or adolescence, and risks declined with increasing age at initial exposure. This age effect has been observed among atomic bomb survivors, those undergoing radiotherapy for benign breast disease, and those undergoing repeated fluoroscopic examinations to monitor tuberculosis (11). The importance of early life exposures has also been demonstrated by studies of the effects of ultraviolet radiation, which causes 90% of basal cell carcinomas of the skin and is an important risk factor for other types of skin cancer (12, 13). Approximately 23% of lifetime ultraviolet radiation exposure occurs before age 18 years (14), and 1 or more blistering sunburns in childhood or adolescence doubles melanoma risk (15). A dramatic rise in the incidence of basal cell and squamous cell carcinomas of the skin among...
women under 40 years of age (16) may reflect temporal increases in time spent outdoors and at the beach early in life (17) and notable use of sunbeds in adolescence and young adulthood (18, 19).

Evidence of the importance of early life events from epidemiologic studies of radiation exposures has fostered an interest in other early exposures that may be related to adult cancers, and the influence of exposures across the life course is increasingly being recognized (20). The approaches used in most epidemiologic studies have precluded assessment of the nature of relationships among exposures over time. Risk factors may associate with each other through tracking of related exposures, as a chain of unrelated exposures, or in an additive or multiplicative fashion to confer risk. Life-course analyses could identify time periods of particular vulnerability (20), which is potentially important for cancers. In this issue, Nimptsch et al. (21) provide an excellent example of an evaluation of high school diet in relationship to colorectal adenomas with adjustment for adolescent and adult energy intakes and other postulated risk factors. Further, the authors combined information from adolescent and adult time periods to evaluate long-term exposure to high or low extremes of intakes and the impact of particular time periods. The thorough and compelling analysis lends credence to the important influence of diet during adolescence. The authors’ extensive efforts to assess the quality of recalled adolescent dietary intake data included assessment of reproducibility within individuals of the high school food frequency questionnaire, comparisons of subjects’ reports with mothers’ recalls, and comparison of 24-hour recalls and 2 youth-oriented food frequency questionnaires with recollection of these data 10 years later by using the high school food frequency questionnaire (22, 23). Such evaluations lend confidence to the data but also identify inherent limitations.

CHILDHOOD AND ADOLESCENT DIETARY EXPOSURES ASSOCIATED WITH INTERMEDIATE MARKERS AND ENDPOINTS

The long latency of cancer has led to the study of biomarkers and precursor lesions thought to be associated with cancers. Examples of such studies, which can inform an understanding of carcinogenesis, are provided below. A low-fat dietary intervention trial in girls aged 8–10 years showed influences on steroid hormone levels during adolescence but not sustained effects on hormone levels measured at ages 25–29 years (24). This finding does not preclude an influence on later risk if adolescence is a vulnerable time period. A questionnaire-based assessment of recalled adolescent diet demonstrated that greater red meat intake, but not other dietary factors, was related to adult breast density in Chinese immigrant women even after adjustment for acculturation (25). Recalled adolescent diet in the Nurses’ Health Study II cohort, the same population studied by Nimptsch et al., showed increased risk of proliferative benign breast disease related to higher animal fat and monounsaturated fat intakes and decreased risk associated with higher vegetable fat, fiber, nu, vitamin E, and vitamin D intakes (26–28). In addition, increased risk of proliferative benign breast disease was linked with recalled adolescent alcohol consumption in a dose-dependent manner (29, 30).

CHILDHOOD AND ADOLESCENT DIETARY EXPOSURES ASSOCIATED WITH CANCER RISKS

Breast cancer studies with recalled soy intake data highlight the importance of assessing the timing of exposure. A case-control study found reduced risk of breast cancer associated with soy intake during childhood, adolescence, and adulthood. The lowest risks, which were associated with childhood intakes, were not attenuated after adjustment for Westernization (31). Among Chinese in Shanghai and Asian Americans, reduced risk of premenopausal breast cancer was associated with high soy intakes in adolescence and adulthood, and risk estimates were markedly lower for those with high soy consumption in both time periods (32, 33).

Energy restriction at various points in the life course has provided evidence of the importance of dietary exposures in early time periods in relationship to cancer or cancer biomarkers. During the Dutch Famine in World War II, severe energy restriction during childhood and adolescence was related to lower risk of adult colorectal cancer (34) and higher risk of breast cancer (35, 36) but not to risk of prostate cancer (37). Unique epigenetic changes were observed in those who experienced famine in adolescence and young adulthood, suggesting persistent changes from early life that may influence adult cancers (38). In another innovative study of energy restriction, hospitalization for anorexia nervosa at ages 10–24 years, but not at ages 25–40 years, was related to reduced risk of breast cancer in adulthood (39).

Several studies showed significant relationships of recalled diet in adolescence with adult cancers. In a case-control study of early onset breast cancer, subjects and their mothers completed an abbreviated food frequency questionnaire about subjects’ diets when they were 12–13 years of age. Among the foods with the best agreement between the mothers and daughters, chicken and fish were linked with increased risk, and fruit and vegetables were associated with reduced risk (40). Higher red meat and fat, but not dairy, fiber, or glycemic load were related to increased risk of adult breast cancer in the Nurses’ Health Study II (41, 42). In the National Institutes of Health–AARP Diet and Health Study cohort, a lower risk of colon cancer was observed for those with higher intakes of vegetables and vitamin A during adolescence but not in adulthood based on recalled adolescent and baseline adult diets (43). Further, higher intakes of nitrate/nitrite from processed meat during adolescence were linked with increased risk of pancreatic cancer among men (44). Recorded data from 7-day household inventories were used as a proxy for individual intakes of family members in the Boyd Orr cohort (45). Although the study is limited in sample size, evaluations of major cancer sites indicated a markedly increased risk of colorectal cancers associated with high childhood dairy intake but no associations with breast and stomach cancers. Although clearly more investigations are needed, these studies suggest that higher animal food intakes during childhood and adolescence were associated with increased risk of some adult cancers, whereas higher intakes of fruit, vegetables, and soy were associated with reduced risks.
OTHER LIFESTYLE EXPOSURES IN ADOLESCENCE AND ADULT CANCER RISKS

High childhood or adolescent body mass has been positively associated with glioma, lymphoma, and colon, colorectal, renal, pancreatic, ovarian, and endometrial cancers (46–50). Weight gain between adolescence and later adulthood also appears to markedly increase the risk of renal and endometrial cancers (46). In some studies, cancer risks related to overweight in adolescence were stronger than risks related to overweight in adulthood (46, 50). Higher body mass in adolescence has been linked with decreased risk of breast and prostate cancers independent of adult weight (51, 52).

High physical activity in adolescence has been associated with lower risk of Hodgkin’s lymphoma, glioma, and colorectal and renal cell cancers (48, 53–57). No associations or slightly reduced risks were observed for adolescent physical activity and endometrial cancers (58–60), and inconsistent findings were observed for prostate and testicular cancers (61–65). Physical activity during adolescence and early adulthood has been associated with lower risk of breast cancer, with a tendency for higher levels of physical activity after age 50 years to be more strongly associated with lower risk of breast cancer (66). Adolescent and lifetime physical activity were not found to be related to adult breast density, suggesting that associations of physical activity with breast cancer may not be mediated through breast density (67). Overall, inverse associations have been consistently noted between adult physical activity and cancers (68, 69), but timing and intensity issues related to physical activity earlier in life have received less attention and remain unclear.

METHODOLOGICAL AND MECHANISTIC ISSUES

Adult cancers most often have a long latency, and the rarity of many site-specific cancers requires large epidemiologic studies. In addition, intermediate markers have not been identified for most cancers. Nonetheless, epidemiologic cancer studies incorporating recalled childhood, adolescent, and early adult exposures and measures of low energy intake and radiation exposure have shown associations with adult cancers.

Recall of a complex exposure such as diet is difficult, and the validity of the recall may be problematic. Relatively low correlations have been observed between recalled diet and earlier recorded dietary intakes \( r = -0.31 \)–\( -0.85 \), with better correlations for food groups than for nutrients or particular foods (23, 70, 71). Diets change over the life course, and data suggest that asking about earlier time periods is preferable to using current diet as a proxy (72). Methods to overcome challenges in capturing past exposures include linking the recall to specific past events (73), evaluating reproducibility of the recalled exposure by the subject or other knowledgeable person (e.g., the mother (22) or sibling (74)), and focusing on the highest-quality variables collected. The use of abbreviated food frequency questionnaires targeted at earlier time periods has limitations, including lack of comparability across studies. Working with cognitive psychologists (75) and developing better questionnaire formats for distant recall may improve recall accuracy. Evaluating the tracking of diet and other exposures across time is essential to identifying critical time periods and to assessing cumulative exposures. To overcome the impediment of the use of different questionnaires for the different time periods, appropriate adjustments and interpretation should help to enhance replication of findings. The complexity of addressing the influence of exposures over time and the relationships among the factors across the life course is acknowledged, but statistical approaches to address this issue continue to evolve.

Registry- and medical record–based studies have been useful for assessing medical conditions, diagnostic and therapeutic radiation, anthropometry, and other exposures in early time periods in relationship to adult cancer risks; however, this approach is limited for dietary intakes. School records or other historical resources potentially could be used to quantify general intakes of the group at that time period followed by assignment of the exposure to an individual by using an ecological approach. Documentation of individuals’ dietary intake data in the distant past would be useful but is available in only a limited number of studies with small sample sizes for cancer outcomes.

IMPLICATIONS AND NEXT STEPS

Opportunities for epidemiologic investigations of the role of childhood and adolescent exposures on adult cancer risk should be sought in existing studies of adults and in cohort studies encompassing lifetime follow-up (e.g., among atomic bomb survivors and the Dutch Famine cohorts). Further work could be pursued in cohorts in which exposures and disease are extensively evaluated in subjects and their offspring (e.g., Framingham offspring and third-generation studies) (76), in studies of offspring of pregnancy interventions (77, 78), and in populations with unique dietary exposures and the potential for long-term follow-up (79, 80). Methodological work relating early diet to identified risk factors for later cancers could be pursued in the newer birth cohorts, but the short length of follow-up and the limited number of known risk factors and intermediate endpoints for cancers may constrain such efforts. Extrapolation of identified adult dietary risk factors and investigation into earlier time periods require identification of additional precursors associated with cancer risk in addition to adenomas and benign proliferative breast disease. Although the evidence linking childhood and adolescent exposures with adult cancer risks is limited, the potential for public health recommendations and interventions underscores the importance of focusing new epidemiologic research efforts on this time period (3, 6).

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