Diet, Nutrition, and the Life-Course Approach to Cancer Prevention[1,2]

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ABSTRACT Cancer results from the interaction of genetic susceptibility and environmental exposures. The diagnosis of cancer is age related; there is a marked increase in cancer incidence after the reproductive years. Nutrient and toxicant exposures are important contributors to the risk of some cancers. Nutrition, as a determinant of growth and body composition, also influences cancer risk, directly due to carcinogens in foods or indirectly by the hormonal and metabolic response to growth and obesity. There is strong evidence that obesity and rapid growth enhance the risk of cancer. The prevention of cancer should start before conception; mothers should start pregnancy with a healthy weight and avoid excessive or low weight gain during pregnancy. Key micronutrients are important for normal embryonic development and fetal growth. Infant growth should be assessed based on optimal health across all stages of the life course, rather than following the present approach of "bigger is better. " This model may increase cancer risk in later life, because bigger is closely linked to fatter. Recent studies of energy expenditure in children indicate that excess energy intakes may have been recommended over the past decades, contributing to the surge in global obesity. Food preferences and habits regarding physical activity and play become set relatively early in life; parents and teachers provide key guidance leading to the adoption of a healthy or an unhealthy lifestyle. Thus, cancer prevention efforts should begin with childhood and continue through all stages of the life course.

KEY WORDS: • *nutrition* • *cancer* • *early diet* • *life course*

After cardiovascular disease, cancer is the second most important cause of premature adult death globally (1). The diagnosis of cancer is age related, with a small peak in the early years of life and a subsequent fall in incidence, followed by a slow rise during adolescence and young adulthood; after the reproductive years, incidence rises markedly (**Fig. 1**). Age-adjusted incidence for some cancer sites (breast and prostate) has increased, suggesting that the observed rise in the proportion of cancer-related death is not due solely to more people reaching old age (2,3). Cancer is the product of the interaction of genetic susceptibility factors and environmental exposures. From an evolutionary perspective, genes responsible for cancer risk before reproduction is completed should be selected out. Conversely, genes expressed after reproductive age cannot be addressed by evolutionary selection. Thus, at young ages cancer is uncommon, whereas at older ages cancer incidence increases (3,4).

Cancer susceptibility is determined by the interaction of multiple genes, thus the consideration that cancer is a genetic disease. However, the occurrence of the disease is strongly determined by environmental factors, such as exposure to ionizing radiation, specific infectious agents, and microbial toxins; dietary factors; and contaminants in food, water, and air (5–7). It has been traditionally thought that, except for the avoidance of carcinogens such as tobacco and ionizing radiation from natural and human-made sources, little can be done to prevent cancer. Despite the acknowledgment that multiple carcinogenic compounds are present in the food supply, only a few have been identified with sufficient certainty to merit regulation. Even then, risk management and control of these substances is of limited effectiveness, because monitoring is uncommon.

Over the past decades, obesity and related metabolic consequences have been recognized as contributory risk factors for some types of cancers. Thus, obesity prevention is increasingly recognized as an important factor in cancer prevention (8–10). Preventing death from cancer has mainly focused on early detection and treatment rather than on modifying the cancer process. More recently, targeted approaches to identify genetic susceptibility have led to preventive measures before any symptoms, signs, or laboratory indicators are present. This article reviews how diet and nutrition throughout the life

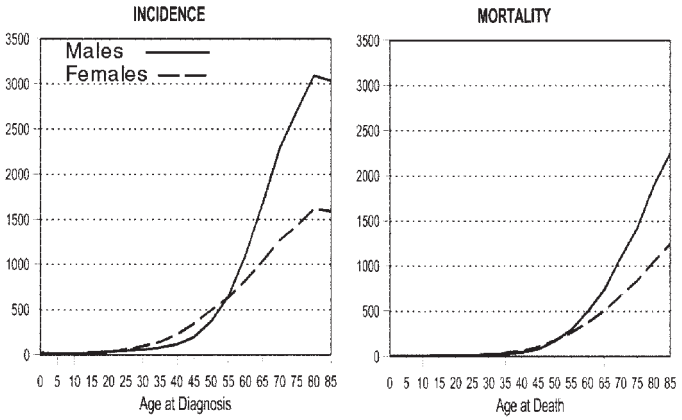

FIGURE 1 Annual cancer incidence and mortality rates per 100,000 persons in New Mexico, 1970–1996; all cancer sites and all races combined. Modified from reference (2).

course can play an important role in primary prevention of cancer (5,11). This approach places a greater emphasis on what can be done at the early stages of life, well before cancer becomes apparent or can be detected by the most sophisticated methods.

We review evidence in 4 key areas. First, we examine how nutrients and toxicants present in foods and water during the early stages of life can contribute to risk for some types of cancers later in life. Second, we explore how diet, as a determinant of growth, body composition, and obesity, can affect cancer risk. Third, we analyze how food preferences and physical activity patterns set in early life may lead to the adoption of unhealthy habits, contributing to enhanced cancer risk. Finally, within an integrated cancer prevention context, we exemplify the life-course approach to cancer prevention, addressing obesity, the major known nutrition (diet and physical activity)-related cancer risk factor.

Nutrient and toxicant exposures and cancer risk

Nutrients and toxicants from food and water constitute important exposures that contribute to the risk of some cancers. The first human evidence that transient exposures to chemical substances during embryonic and fetal life could trigger cancer in offspring came in 1970, when Herbst et al. (12) reported 7 cases of clear-cell adenocarcinoma in young women aged 15–22 y, all seen at a single hospital in Boston. All 7 women were mothers and shared the antecedent of treatment with diethylstilbestrol during the first trimester of pregnancy. This drug had been used therapeutically in early pregnancy in the belief that it would reduce the incidence of premature births and neonatal deaths. Alerted to this association, Herbst established a registry addressing the risk for transplacental carcinogenesis, which documented that all but a few cases showed an association between vaginal adenocarcinoma and diethylstilbestrol exposure. These observations alerted physicians and others to the potential adverse consequences of exposure to toxic substances during pregnancy.

Developing organisms have increased susceptibility to cancer if they are exposed to environmental toxicants during rapid growth and differentiation. Human studies have demonstrated clear increases in cancer after prenatal exposure to ionizing radiation, and some evidence indicates that brain tumors and leukemia may be associated with parental exposure to chemicals. Animal experiments have demonstrated increased tumor formation induced by prenatal or neonatal exposure to various chemicals, including direct-acting carcinogens and drugs. Synthetic halogenated chemicals increase liver tumors after exposure during early life. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin, a prototypical endocrine-disrupting compound present as a contaminant in food and water, is a developmental toxicant of the mammary gland in rodents (13). Dioxins alter multiple endocrine systems, and their effects on the developing breast involve delayed proliferation and differentiation of the mammary gland as well as an elongated window of sensitivity to potential carcinogens (13). These new findings imply that endocrine-related cancers or susceptibility to cancer may result from developmental exposures rather than exposures existing at or near the time of tumor detection. Recently, natural estrogens have been classified as known human carcinogens. Prenatal exposure to natural and synthetic estrogens is associated with increases in breast and vaginal tumors in humans as well as uterine tumors in animals (14).

The relevance of these findings to human cancer is further supported by recent observations on human newborns. Umbilical cord blood from newborns was assayed for 413 chemicals, pesticides, and other pollutants; 287 pollutants were detected in close to 70% of those tested (15). Of these 287 chemicals, 180 are carcinogens to humans or animals, 217 are toxic, and 208 cause disruption in normal embryonic growth and fetal development. Moreover, the risk of combined exposure to these chemicals [organochlorine pesticides (present in a wide range of home products); perfluorochemicals, brominated fire retardants, and polychlorinated biphenyls (from waste incineration and fossil fuel combustion); polyaromatic hydrocarbons; polychlorinated and polybrominated dioxins and furans; polychlorinated naphthalenes; and mercury] is not fully known. These data support a life-course approach to cancer prevention.

Direct and indirect effects of diet and nutrition on cancer risk

The effect of diet can be direct, via the cumulative effect of exposure to nutrients and carcinogens in foods; in this case, the balance of cancer-promoting and -protective substances may contribute in defining cancer risk (8–11). There are also indirect ways by which diet affects the cancer process. These include the effects of diet on energy balance and risk of obesity and the hormonal and metabolic responses related to energy balance. The latter are associated with the metabolic syndrome and the inflammatory mediators linked to increased adipose tissue. In addition, diet as a determinant of growth and body composition may influence cancer risk both directly by affecting tissue growth itself and by affecting trophic hormones that mediate the growth process. Trophic hormones can influence the growth process and thus increase cancer risk. Obesity and rapid growth at critical times may increase the risk for some types of cancer; conversely, energy deficit and leanness my have a deleterious or protective effect for some cancers, depending on the timing or the tissue-specific effects of the nutritional deprivation (9,10). Some infectious agents acquired through contaminated diets can affect cancer risk, such as chronic *Helicobacter pylori* infection, which induces inflammation of the gastric mucosa and thus affects cancer risk (7).

Overall food intake (total energy). The follow-up of a large cohort with carefully measured dietary intakes during childhood has served to evaluate the potential effect of energy intake on adult mortality from cancer (16). The study included 3834 adults who were part of Lord Boyd Orr's Carnegie

TABLE 1

Mean age-specific energy intake according to distribution of daily energy intake

Age group	Energy intake	
	Lowest fifth	Highest fifth
y	*MJ/d (kcal/d)*	
<1	2.65 (633)	4.75 (1137)
1–3	3.70 (866)	6.65 (1592)
4–9	5.82 (1393)	10.45 (2501)
10–14	7.59 (1815)	13.62 (3259)

survey of family diet and health in England and Scotland between 1937 and 1939. The group's diet was evaluated during 1 wk using standardized methods and was followed up for cancer occurrence through the National Health Service central register. Significant associations between childhood energy intake and adult cancer mortality were observed, taking the confounding effects of social variables into account in proportional hazards models. The relative hazard for all cancer mortality was 1.15 (95% CI: 1.06, 1.24; $P = 0.001$) for every 1 MJ increase in adult equivalent daily intake. The effect was observed only in cancers unrelated to smoking (relative hazard 1.20; CI: 1.07, 1.34; $P = 0.001$) in both men and women. **Table 1** provides summary information on the distribution of energy intake in childhood and **Table 2** presents adult cancer risk according to early energy intake and smoking category (16).

The data from this study are consistent with animal studies showing that energy restriction reduces the risk of cancer (8–10). The limited epidemiological evidence for long-term effects of early diet suggests that defining optimal childhood nutrition is important. The data indicate that higher energy intake in childhood may increase the risk of developing cancer in adult life. The latest FAO/WHO report on human energy needs in fact reexamined the energy needs of children based on actual energy expenditures and established recommended energy intake levels that are 10 to 20% lower than presently advocated for children ages 0 to 10 y (17).

Information on the effects of acute famine on cancer risk is also available. For this review, we have chosen to ascribe these effects to overall food or energy deficit rather than to deficit of a particular specific nutrient. The most compelling data originate from the Dutch famine studies, referring to the acute drop in food availability in western Holland during the last months of the Nazi occupation (October 1944 to May 1945). Mean energy available per person dropped from about 1800 kcal/d (7.53 MJ/d) to as low as 600 kcal/d (2.51 MJ/d) at the worst time of the famine. In addition to preserving detailed records on available foods, rationing efforts permitted dietary intakes to remain as good as possible given the circumstances (18,19). The account provided by the author of this unique study suggests that because few cases of overt micronutrient malnutrition were found immediately after the war, the famine had not fully depleted essential nutrient reserves. Increased mortality was limited to elderly males and very young children; thus, women in the reported diagnostic cohorts who were older than 2 y during the famine most likely reflect the situation of most survivors. Breast cancer screening mammograms, assessed for all women included in the study, were classified by amount of dysplasia, coded as the proportion of the breast occupied by radiodense tissue and expressed as a dichotomous variable (yes if ≥50% dysplasia; no if <50%). The relations between famine exposure and its effects on mammographic patterns were determined as summarized in **Table 3**. The findings indicate that famine exposure before age 10 y affects dysplasia levels later in life. Women exposed before this age had less dysplasia, whereas women exposed after age 18 y had more dysplasia, compared with nonexposed women of the same ages. Famine exposure had a differential effect as a risk factor depending on the timing relative to breast development, lowering the risk in women exposed before puberty and increasing it in women exposed after completion of breast growth (18,19).

TABLE 2

Effect of energy intake during childhood on adult mortality, derived from age-adjusted and fully adjusted models of energy intake as a continuous variable[1,2]

Cause of death	Age-adjusted model	Fully adjusted model
All causes	0.99 (0.96, 1.02)	1.04 (0.99, 1.09)[3]
All cancers	1.05 (0.99, 1.11)	1.15 (1.06, 1.24)[4]
Cancer not related to smoking	1.07 (0.99, 1.15)	1.20 (1.07, 1.34)[4]
Cancer related to smoking	1.02 (0.94, 1.11)	1.09 (0.96, 1.23)[5]

[1] Modified from Frankel et al. (16).
[2] Both sexes ($n = 3834$). Values are hazard ratios (95% CI); fully adjusted models of energy intake as continuous variable on mortality per MJ/d (239 kcal/d), adjusted for age, household expenditure, social class, number of children, and time since survey.
[3] $P = 0.11$.
[4] $P = 0.001$.
[5] $P = 0.18$.

TABLE 3

Risk of breast dysplasia by famine exposure and age at time of exposure[1]

Age at exposure	*n*	Odds ratio (95% CI)
y		
2–9	6,560	0.83 (0.65, 1.06)
10–12	2,560	1.02 (0.72, 1.44)
13–18	3,586	0.96 (0.72, 1.27)
>18	7,024	1.32 (1.14, 1.53)[2]
Overall, 2–33	19,730	1.16 (1.04, 1.29)[2]

[1] Modified from van Noord (18).
[2] $P < 0.05$.

Attained weight (underweight and overweight). Data from multiple large prospective studies show a significant association with obesity for several cancers. This evidence has been classified as convincing for cancers of the colon, female breast (postmenopausal), endometrium, kidney (renal cell), and esophagus (adenocarcinoma). The rising worldwide trend in obesity suggests that overeating may be the largest preventable cause of cancer in nonsmokers. Obese adults are largely unsuccessful in long-term weight reduction; thus, early prevention of obesity is crucial to cancer risk reduction. Obese children have an increased probability of becoming obese adults, especially when parents are also obese (20). This by itself defines the need to avoid excess weight in childhood. However, there is limited evidence that obesity at an early stage of life by itself entails greater risk of adult cancer.

There is some evidence for early obesity, assessed by weight-for-height indexes such as BMI, as a risk factor for cancer (colon and breast). However, data supporting this relation are difficult to interpret, because early obesity is also linked to increased risk of adult obesity. Thus, the effect of early obesity on cancer risk cannot be fully separated from that of concurrent obesity. The data from the Harvard growth study analyzed by Dietz (21) indicates that colon cancer mortality increased 9-fold for men who were obese during adolescence. Studies on the long-term effects of childhood obesity on adult disease are also confounded by the presence of other potential risk factors, including completion of fewer years of education, higher rates of poverty, and lower rates of marriage and household income. The effects may be related both to the persistence of obesity and to the effects of childhood or adolescent obesity on the quantity and location of adult body fat deposition. Studies to date have failed to measure visceral fat or to include valid measures of total body fat. Thus, it is not clear whether the effects of visceral fat on morbidity are independent of the effects of total body fat. Total body fat in children and adolescents may be a more powerful predictor of morbidity than regional fat deposition. Distribution of body fat and the associated metabolic consequences may be affected by the age or developmental stage of the child. This may have implications for cancers linked to estrogen activity, such as breast cancer. The effects of obesity have not clearly been distinguished from the factors that promote obesity or the regional deposition of fat, for example, pattern of food consumed or level of fitness (20,21).

Attained stature (height). Adult height is associated with cancer risk for some sites, prominently for the breast and more weakly for other sites, such as the prostate and colon. The mechanisms underlying this association are complex: adult height is positively correlated with birth weight; growth rate; and age at puberty, which is negatively associated with breast cancer risk.

Several studies attempted to unravel this relation. Prospective data from a British cohort of 2547 girls followed from birth in 1946 to the end of 1999 to examine breast cancer risk in relation to childhood growth sparked interest in this topic. In the initial study, adult height was positively associated with age at menarche and breast cancer. In a follow-up analysis, random coefficient models were used to estimate the individual trajectories in height and BMI up to age 7 y. The parameters identified by these models were then included to assess the effect of birth weight together with timing of menarche. Birth weight was found to positively influence height and BMI values at age 2 y but not to affect their rates of change from ages 2 to 7 y. Low weight at birth was associated with an early onset of menarche, but after controlling for growth in infancy this effect was reversed, so that girls who were heavy at birth reached menarche earlier than others with similar growth in infancy. Rapid growth in infancy was also related to early puberty. The effects of these variables were particularly marked in women with early menarche age (younger than 12.5 y). The findings were interpreted to suggest that women who grow faster in childhood and reach an adult height above the average for their menarche category are at a particularly increased risk of breast cancer. The findings are consistent with the notion that timing of menarche may be set in utero or early in life, although it may be modified by changes in body size and body composition in childhood (22,23).

Associations among stature, BMI, and cancer were also explored in a Norwegian cohort of 2 million people from 1963 to 2001. For esophageal cancer, men of low stature had the highest risk in general, whereas differential effects for BMI were found for different histological subtypes. Compared with subjects with normal BMI, an increased risk of esophageal adenocarcinoma was observed in overweight and obese men and women, whereas the opposite relation was observed for esophageal squamous cell carcinoma (24). However, data from a prospective cohort of South Korean men used to examine the relation of adult height with all-cause mortality showed no linkage of cancer death with adult height (25). This study of 386,627 middle-aged male civil servants from 1992 to 1998 demonstrated an inverse association between height and all-cause mortality (14,003 deaths) after adjustment for socioeconomic position and major behavioral risk factors. The adjusted relative risk for all-cause mortality associated with a 5-cm increment in height was 0.97 (95% CI: 0.95, 0.98). There was little evidence of association between height and coronary heart disease or overall cancer mortality. However, stomach cancer showed a weak inverse association that was attenuated after adjustment.

Growth attainment (weight and height) and trophic factors. Information on the effects of altered growth due to acute famine on cancer risk is available from the Dutch famine cohort study. As indicated previously, we ascribed these effects to overall food or energy deficit rather than to deficit of a particular specific nutrient. The effect of famine in early life on increased breast cancer risk was greatest in women who had been exposed to famine between ages 2 and 9 y; however, this effect was modified by parity status (18,19). The effect of early famine among nulliparous women was twice as large as that among parous women, as reflected by a hazard ratio of 2.02 (95% CI: 0.92, 4.42) for nulliparous women compared with 1.38 (95% CI: 0.99, 1.93) for parous women. The protective effect of pregnancy partly mitigated the adverse effects of famine exposure. Additional univariate analyses of associations found that famine-exposed women were slightly shorter and had a later menarche than unexposed women. Although these early risk indicators, height and menarche, had moved in a preventive direction, the magnitude of these protective effects was not sufficient to modify the end result of increased breast cancer risk for the group exposed at ages 2 to 9 y. Within the cohort, women who were slightly shorter and had a later menarche than unexposed women had a decreased risk of breast cancer, thus reflecting effects seen in the whole cohort.

These observations may be explained by the interaction among dietary energy, endocrine responses, and human cancer risk. A developmental approach to cancer risk, as opposed to a risk factor approach, can better explain why at certain ages there may be periods of especial sensitivity to diet changes even before there is significant breast development. Moreover, we need to consider that these effects could have transgenerational consequences; exposure of women to famine could also affect their unexposed offspring (18,19). These observations have important implications for preventive strategies; for example, avoiding excess weight and rapid growth in girls as they approach puberty and extreme thinness postpuberty could have beneficial effects for preventing breast cancer. They also suggest the need to include cancer risk as an outcome as we attempt to define optimal growth on the basis of both short- and long-term health effects.

Further information on the association between growth during childhood and the risk of breast cancer is provided by a cohort of 117,415 Danish women born from 1930 to 1975 in the municipality of Copenhagen (26). School health records provided information on annual weight and height measurements, age at menarche, and birth weight as reported by the parents. These data served to model individual growth curves.

TABLE 4

Growth during childhood and risk of breast cancer[1]

Growth variable	Relative risk (95% CI)[2]		Comparison[3]
	Age < 50 y	Age ≥ 50 y	
			P
Birth weight[4]	1.14 (1.01, 1.28)*	1.05 (0.91, 1.21)	0.39
Age at peak growth[5]	0.90 (0.86, 0.95)*	0.98 (0.93, 1.03)	0.03
Age at menarche[6]	0.98 (0.88, 1.08)	1.01 (0.87, 1.17)	0.74
Height at age 8 y[5]	1.11 (1.05, 1.17)*	1.11 (1.05, 1.17)*	0.62
Height increase ages 8–14 y	1.15 (1.05, 1.27)*	1.18 (1.07, 1.30)*	0.74
BMI age 14 y[5]	0.95 (0.93, 0.97)*	0.94 (0.92, 0.97)	0.22

[1] Modified from Ahlgren et al. (26).
[2] Relative risk calculated per kg increase in birth weight per y increase in age at peak growth and age at menarche; per 5-cm increase in height; and per unit increase in BMI. * $P < 0.05$.
[3] Difference in relative risk before and after age 50 y.
[4] Adjusted for age at peak growth, height at age 8 y, height increase from ages 8–14 y, and BMI at age 14 y. Further adjustment for age at menarche did not markedly change the estimate.
[5] Mutually adjusted. Further adjustment for birth weight and age at menarche did not markedly change the estimate.
[6] Adjusted for age at peak growth, height at age 8 y, height increase from ages 8–14 y, and BMI at age 14 y. Further adjustment for birth weight did not markedly change the estimate.

Information on vital status, age at first childbirth, parity, and diagnosis of breast cancer was obtained through linkages to national registries; 3340 cases of breast cancer were diagnosed during the 3,333,359 person-y follow-up. **Table 4** summarizes the results: high birth weight, high stature at age 14 y, low BMI at age 14 y, and peak growth at an early age were independent risk factors for breast cancer, affecting mainly premenopausal women. Height at age 8 y and the increase in height during puberty (ages 8–14 y) were associated with breast cancer in women before and after age 50. The protective effect of a high BMI at age 14 on breast cancer contrasts with studies showing that overweight in girls is associated with early menarche, because a higher breast cancer risk would be expected with earlier menarche. The findings of the Danish study suggest that the effect of childhood obesity on breast cancer is not caused by the acceleration of puberty, because in this study early menarche had the opposite effect of obesity. However, the estrogens produced by adipose tissue may promote earlier differentiation of the breast epithelium (26,27). Further analysis assessing the size of the effect and the prevalence of the specific risk conditions indicates that overall population attributable risks of birth weight, height at age 14 y, BMI at age 14 y, and age at peak growth were 7, 15, 15, and 9%, respectively. No effect of adjustment for age at menarche, age at first childbirth, and parity was observed. The authors concluded that birth weight and growth during childhood and adolescence influence the risk of breast cancer (26).

Endogenous hormonal responses or potentially exogenous dietary factors with hormone-like properties could partly explain these findings, because they can affect susceptible mammary tissue at critical times (27). This becomes especially relevant because recent studies indicate that milk consumption increases the circulating levels of insulin-like growth factor (IGF)-1 and is associated with higher stature (28). High insulin and IGF-1 levels are increased by the high protein and energy intakes typical of modern diets. The interactions of these hormones with the hypothalamus-gonadal axis define free circulating estrogens that may link the nutritional-metabolic status with endocrine maturation of reproductive functions and may affect the risk of cancer. Circulating blood IGF and sex hormone levels are modulated by their binding proteins. IGF-binding proteins and steroid hormone–binding globulin are in turn modulated by both insulin levels and diet. High circulating insulin lowers sex hormone binding globulin, increasing available free estrogens for tissue binding. IGF-1 was recently strongly associated with the risk of breast cancer (29). IGF-1 is a potent inducer of mitosis, operates estrogen receptors, controls progesterone receptors, and in synergy with estrogen stimulates the growth of human breast epithelial cells. As the mammary gland develops and matures, it undergoes hyperplasia (cell replication), which is regulated in part by IGF-1 and estrogens. During stages of rapid cell division, there is increased opportunity for mutations to occur.

A recent report from the United Kingdom on the follow-up of persons treated with human growth hormone, examining their risk of cancer, further supports the role of IGF-1 and related growth factors in cancer risk (30). Growth hormone action raises serum concentrations of IGF-I. Patients treated with human pituitary growth hormone had significantly increased risks of mortality from cancer overall (standardized mortality ratio 2.8; 95% CI: 1.3, 5.1; 10 cases), colorectal cancer (10.8; CI: 1.3, 38.8; 2 cases), and Hodgkin's disease (11.4; CI: 1.4, 41.3; 2 cases). Incidence of colorectal cancer was also greatly increased (7.9; CI: 1.0, 28.7; 2 cases). After exclusion of patients whose original diagnosis rendered them at high risk of cancer, the significance and size of the risks of colorectal cancer incidence and mortality and of Hodgkin's disease mortality were increased.

It has been suggested that the trend toward faster growth and earlier age at menarche among girls living in industrialized and transitional countries is linked to an increased incidence of some cancers. Breast cancer is thought to be related to high lifetime exposure to free estrogen. The earlier a girl starts menstruating, the more menstrual cycles she will have, and the greater will be her exposure to estrogen during her childbearing years. Height, weight, diet, exercise, and family history have all been found to influence age at menarche. Taller, heavier girls generally start menstruating earlier than shorter, lighter girls. In addition, the distribution of body fat is related to circulating hormone levels and may affect age at menarche. Girls with abdominal fat are more likely to be obese and to have higher insulin levels. Increases in insulin and growth

hormone influence the levels of IGF-1, which may promote hyperplasia in breast tissue (27,29). The effect of a rapid rate of growth during early adolescence may be of special interest, because it is a potentially modifiable risk factor; moreover, rapid growth at this stage of life does not appear to have advantages for other health outcomes. These results provide strong evidence that regulatory factors influencing fetal, childhood, and adolescent growth are potentially important independent risk factors for breast cancer in adulthood. Therefore, exposures or factors that condition growth during these periods, such as diet and physical activity, are of particular importance in relation to adult breast cancer.

Life-course implications of early establishment of food preferences and selection and physical activity patterns

It is clear from the two preceding sections that the balance between total energy intake and net energy expenditure, the equation that determines body mass and influences the hormonal regulation of growth, is a key factor in the occurrence of cancer within an individual. However, the specific constituents of the diet and their chemical and nutrient composition—what we can call the quality of the diet—are also important in the genesis of neoplastic disease. Doll and Peto (8) estimated that 30% or more of human cancers could be attributed to dietary factors. The past quarter of a century has provided substantial evidential validity for the proposition that certain foods and components of foods can promote or retard the initiation and progression of carcinogenesis (9,10).

The physical activity pattern is also important for more than just the expenditure of energy. Clearly, one can have exactly the same daily energy output with slow but steady light activity throughout the day as with bursts of vigorous activity interspersed with prolonged sedentary periods. Hence, characteristics such as the intensity, duration, and frequency of activity and whether it is part of occupational tasks, housework, or sport and recreation may moderate its health effects (31,32)

Food preferences and selection. Inherent in the Doll and Peto (8) synthesis is the assumption that consumption of certain foods promotes the occurrence of cancer, whereas other foods have a protective effect. The adverse or beneficial effects of dietary foods and beverages have generally been attributed to their chemical constituents.

Setting the pattern of tolerance and dietary diversity in early life. To consume the elements of a healthful and cancer-preventive diet, one must be willing to incorporate the appropriate food items into one's habitual fare. The tolerance of—if not the preference for—a diverse variety of foods is established early in life (33–35). The greater the net variety of species in the diet, the less intense the exposure to any one of them that might have a carcinogenic potential. This is a first principle for encouraging young children to consume a wide array of dietary items, especially of plant origin.

Young children have an innate attraction to sweet and salty flavors and an aversion to bitter and sour tastes (33). Plant-based phenols, polyphenols, flavonoids, isoflavones, terpenes, and glucosinolates, which are considered to represent some of the natural cancer-protective phytocompounds, are bitter, acrid, or astringent in taste and therefore aversive to the consumer (36). This represents a challenge in setting a healthful eating context early in life.

Children tend to be afraid of new foods and do not readily accept them (35). As summarized by Birch (33): "their preferences for the majority of foods are shaped by repeated experience . . . the predisposition to learn to prefer and accept new foods when they are offered repeatedly. In addition, the predisposition for associative conditioning affects children's developing food acceptance patterns, resulting in preferences for foods offered in positive contexts." Parents influence children's eating patterns through their behaviors, attitudes, and feeding styles, and it is important to make healthy food choices available in positive mealtime situations (36).

Epidemiological evidence combined with feasible mechanistic constructs suggests that fruits, vegetables, and unrefined cereals, pulses, and starchy foods protect against many human cancers (9,10). A salient example of this relation between an epidemiological association with cancer prevention and bolstering experimental evidence for in vitro and in vivo mechanisms of action is that of tomato consumption and its reduction of prostate cancer risk (37,38). Here, the primary chemical agent was thought to be the carotenoid lycopene. On the mechanistic side was the demonstration of lycopene as an in vivo antioxidant, enhancing cell-to-cell communication by increasing gap junctions between cells and modulating cell-cycle progression (37). Moreover, tomato supplementation significantly diminished oxidative DNA damage in leukocytes and prostate tissues, and there was a decrease in blood prostate-specific antigen in the patients, which was explained by the increase in apoptotic death of prostate cells, especially in carcinoma regions (38). Notably, however, whole tomato—with all of its various nutrients and phytochemicals in balance—may have more anticancer properties than simply the lycopene alone (37).

Corroborating the notion of early establishment of protective eating patterns are suggestions from a literature review by Tsubura et al. (39) on (n-3) fatty acids and fruits and vegetables in the reduction of breast cancer risk. The authors conclude that "time of intake appears to be important: lifetime protection may be achieved if one is exposed to a dietary factor that lowers breast cancer risk early in life." This is bolstered by the findings that the origins of human breast cancer begin very early in a woman's life (40,41). Hence, its prevention must commence at a comparable stage.

Adverse imprinting on fast-food restaurant fare in early life. Expenditure on foods in so-called fast-food restaurants has increased >15-fold over the past 2 decades in the United States. Selections from these popular food outlets are readily accepted by children. Birch (33) comments: "Children also learn to prefer energy-dense foods when consumption of those foods is followed by positive postingestive consequences, such as those produced when high-energy-density foods are eaten when hungry." Aside from the high energy densities and large portion sizes for which this class of cuisine is notorious, the features of high-temperature cooking; high fat intake in meats and fried potatoes; sugary beverages and desserts; and the offering of red and cured and salted meats run afoul of at least 5 of the World Cancer Research Fund/American Institute for Cancer Research recommendations for dietary cancer prevention (42). Experience with such fast foods can also shape long-term food preferences from early in life. Not only is it important to develop a tolerance and appreciation for the widest range of tastes and foods from early in life, but guidance away from the salty, sugary, fatty, and meaty fares that typify classic fast-food menus is an important part of education for nutritional health.

Patterns of meal frequency and potential implications for health. Not only the selection of foods items but also the meal frequency throughout the day are habits that may be learned and imprinted early in life by family routines. Carnivores in nature, dependent on killing prey, eat sporadically, whereas herbivores graze on plants during much of the 24-h

cycle. Humans are omnivores, consuming both flesh and plants as part of a balanced diet, but they can do so with large servings within a limited number of mealtimes (gorging) or with frequent small repasts (nibbling). Putative health implications arise within the context of meal frequency, some of which may have implications for carcinogenesis (43).

It has long been appreciated that nibbling or gorging could influence intermediary metabolism of dietary fuels (44). Meal frequency may even have some influence on the metabolism of individuals with rigorous exercise regimens (45,46). The influence of meal frequency on immune function has recently been addressed, raising a potential link with immunovigilance against precancerous cells. To what extent there is early-life imprinting of meal-frequency patterns for later life remains to be studied. This is an area of ongoing investigative inquiry that needs to be followed closely, given the potential health implications of nibbling or gorging habits throughout the life course.

The crucial nature of the life stage for protective exposure. This can be exemplified in relation to essential fatty acids in the diet. There has been growing interest in the association between consumption of (n-3) fatty acids and reduced risk of certain hormonal cancers, such as those of the breast and prostate (47). These dietary substances are also attributed with protection against cancer of the large bowel (48). The habit of eating marine fish and fish oils would favor a higher (n-3):(n-6) ratio in the diet and in blood and tissues. The importance of the life-course timing of dietary (n-3) fatty acid consumption is illustrated by an ecological analysis of fish consumption patterns in 24 European countries (49). Current consumption of fish and fish oil had an inverse association with colorectal cancer mortality ($P = 0.036$), as did their consumption 10 y ago ($P = 0.042$), whereas no significant relation was found with consumption 23 y ago. The authors concluded that fish consumption is associated with protection against the later promotional stages of colorectal carcinogenesis but not with the early initiation stages. In terms of mechanisms of protection, they point to a role for prostaglandins, derived from (n-3) fatty acids, in colorectal carcinogenesis.

Physical activity patterns. The mechanisms by which a pattern of physical activity favors or disfavors a particular cancer are poorly understood.

Early-life determination of physical activity patterns. When intense physical activity is part of leisure-time recreational activities, early encouragement to participate in individual or team sports may condition children to engage in recreational sports throughout life. Those who develop an aversion to rigorous play in childhood may likewise continue this throughout life. On the other hand, among those positively disposed toward recreational sports, economic and environmental constraints in later life may interfere with participation. Whatever the initial patterns of play and physical activity in early childhood, there is a tendency toward lesser activity from ages 10 through 20 y. In a longitudinal study of 2379 white and black U.S. girls, beginning at age 9 y and following them to age 18 y, a 22% reduction in physical activity was observed, independent of ethnic heritage (50)

For most individuals, however, the pattern of physical activity may be more a function of the prevailing opportunities for transport, household maintenance, and productive employment in a given stratum of society. Automation and mechanization in each of these domains would condition individuals toward a more sedentary existence, whereas the absence of powered machines and reliance on human physical effort to move about, maintain the home, and earn a living would have the opposite effect. The term *lifestyle* as a framework for the usual activities of daily life is now recognized as a partial misnomer. Where individuals have the luxury to choose how much physical effort they exert, how they lead their overall lives may indeed be considered as style. However, where conditions of poverty and lack of choice oblige individuals to perform a universal set of tasks, "lifestyle" might better be termed *life determination*. Ironically, however, where mechanization and automation are absent and drudgery is the lifelong order of the day, the full spectrum of intensity of physical activity is likely to be practiced frequently and for long periods just to survive in a harsh environment.

Physical activity patterns and cancer risk. The greatest current discussion and research on physical activity and inactivity and the origin of human cancer revolve around cancers of the thyroid, ovary, prostate, colon, and breast (51). Specifically with respect to human breast cancer, the texture of the activity pattern characterizes the protective effect. Friedenreich and Orenstein (52) established that moderate-intensity physical exertion by adult women in occupational and household activities contributed more to reduction in breast cancer risk than did any form of high-intensity recreational or sports participation.

In conjunction with our life-course perspective, an issue of timing of the protective physical activity has emerged. Lagerros et al. (53) at the Karolinska Institute in Sweden sought to produce a quantitative literature review focused on moderate to vigorous recreational activity among adolescent and young-adult women. The issues were the consistency of a protective relation with breast cancer risk and assessment of any dose-response effect of the exercise. They analyzed a compilation of 19 case-control and 4 cohort studies published across the 36-y interval from 1966 to 2002. The summary relative risk from the random effects model was 0.81 (95% CI: 0.73, 0.89), almost a 20% risk reduction, which proved to be fairly consistent despite variation in populations and methods (54). Physical activity in females ages 12 to 24 y significantly reduces the risk of breast cancer. Overall, the regression analysis indicated that for each 1-h increase in recreational participation, there was a 3% reduction in breast cancer risk across the pooled literature sample.

We suspect that beyond maintaining voluntary active energy expenditure >75% of basal energy expenditure, equivalent to a physical activity level of 1.75 (42), practicing certain patterns of activity will protect against certain cancers (31,32). More evidence is needed, and appropriate exercise and activity routines that are compatible with all life pursuits and occupations must be developed. It will be a lifelong challenge for each individual to adopt and maintain the most favorable physical activity practices, especially in affluent societies in which motorized transportation and the use of mechanized labor-saving devices are the norm. In such societies, leisure-time physical activity (LTPA) may be the true differential in energy expenditure and hormonal regulation by activity. A case-control study of 81% of all deaths among Hong Kong residents over age 35 y ($n = 24{,}079$) in 1998 found an inverse association between LTPA frequency and all-cause mortality and specific mortality from cardiovascular causes and cancer separately (54). Moreover, for each category of increasing LTPA from 1 time per month to 4 times per week, there was a graded protective effect after adjustment for age, educational attainment, smoking status, alcohol use, and even the physical demand at the workplace. The protective effect against death from cancer was lower than for death from respiratory and cardiovascular disease. Overall, however, the authors conclude that one-fifth of all deaths in those aged ≥35 y in Hong Kong in 1998 were attributable to physical inactivity, which ex-

ceeded tobacco-related mortality in this population. The authors reflect on the social and demographic changes occurring in the rest of their vast nation and predict that mainland China will witness a similarly large mortality burden in the next few decades as it undergoes further socioeconomic development.

Cancer prevention: a comprehensive life-course approach

Examining the immediate, underlying, and basic causes of cancer. We can not yet fully ascertain the direct causal pathway for most human cancers, but we are certain that cancer is not a random event in the human life course (5,8,42). Our present understanding of molecular regulation of gene expression and how environment and genes interact in defining normal and neoplastic cell growth permits us to unravel how the cancer process is initiated and what can trigger expansion of abnormal cell clones (55–57). As shown at the bottom right of **Figure 2**, hormones and growth factors mediated by receptor and signal transduction systems end up regulating the expression of genes responsible for cell growth and replication. This simplified picture allows us to model the interaction of environmental factors, including diet, with the genetic determinants (seldom monogenic, frequently polygenic) that ultimately determine cancer incidence (55–57). Much of present research is centered on clarifying these mechanisms. This is undoubtedly a valid approach from the standpoint of defining how the cancer process works and possibly how to intervene with treatment and preventive strategies (58). Within the epigenetic factors, as shown at the top right of Figure 2, diet- and nutrition-related factors play an important role in defining cancer susceptibility (5–11). As indicated in earlier sections of this review, rate of growth, body composition, and diet macro- and micronutrient content are important in defining cancer risk for some sites. The metabolic consequences of obesity and the concomitant inflammatory response have been linked to altered hormonal profiles, with consequences for normal and abnormal cell growth and possibly for the expansion of tumors (55–58). Nutrients also play important roles in defining the immune response, including natural killer cells, metabolic capacity to detoxify chemicals, and response to drugs with carcinogenic potential (5,6). Recent evidence also indicates that nutrients interact by themselves or affect the way other chemicals interact with the genetic material, modulating what genes are expressed and to what degree they are expressed (57–60). In other cases, such as with vitamin K–dependent carboxylation, nutrients modify the expressed proteins after translation (61).

A major proportion of our human and material resources are presently being spent in advancing the knowledge base to understand what cancer is and how the cancer process develops. Undoubtedly, we can rationalize spending even more resources in addressing these issues; however, the question is whether we should in parallel begin to explore the underlying factors and basic causes that condition the exposures that in turn become the epigenetic factors affecting the genetic determinants of cancer. The middle and left boxes of Figure 2 define some of the most relevant problems (i.e., that we can do something about) that most likely underlie the preventable causes of cancer. Progress in cancer prevention will most likely come from what we are able to do in addressing these through effective policies and programs rather than from refining our scientific knowledge of the cancer process itself.

The life-course approach to cancer prevention. Start early; act at all stages of the life course (**Fig. 3**). Life-course prevention of cancer should start before conception; mothers should start pregnancy with a healthy weight for their height and avoid excessive or low weight gain during pregnancy. Key micronutrients such as folate, iron, copper, zinc, and vitamins are important for normal embryonic development and fetal growth. Infant growth should be based on optimal health across all stages of the life course; as previously indicated, this has yet to be established (62). The present bigger-is-better model may increase cancer risk in later life, because bigger is closely linked to fatter (20,62). Moreover, recent assessments of the energy needs of children suggest that over the past decades 15 to 20% excess energy intakes have been prescribed, contributing to the surge in obesity observed globally and

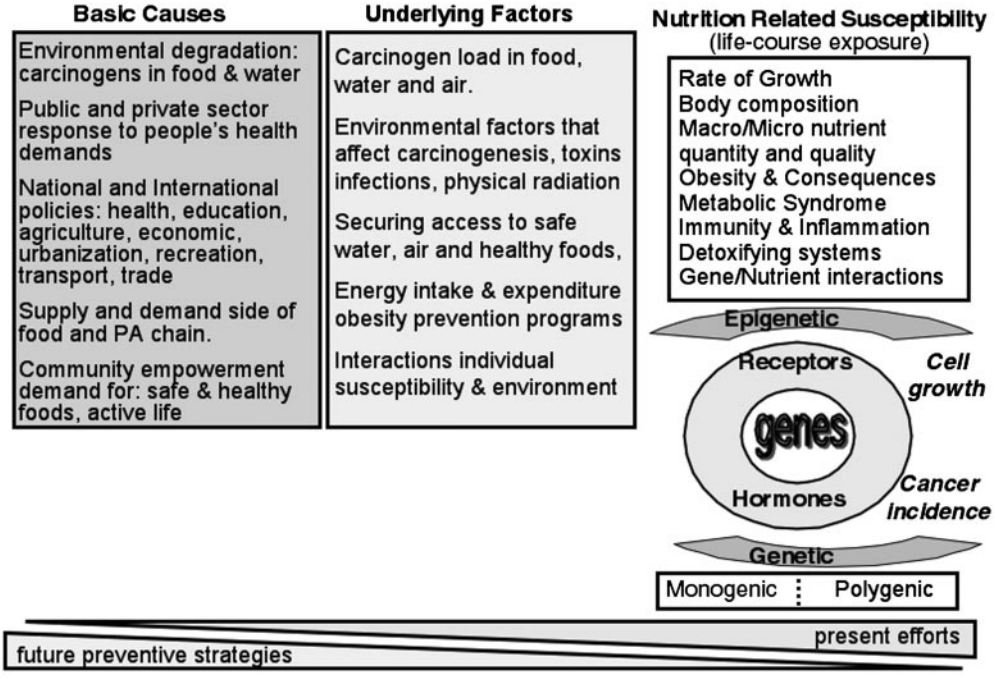

FIGURE 2 The basic causes (*left box*) and underlying factors (*middle box*) that determine nutrition-related susceptibility to cancer (*right box*) model the interaction of environmental factors, including diet, with the genetic determinants (seldom monogenic, frequently polygenic; *lower right*) that ultimately determine cancer incidence. The three boxes illustrate where and how possibly to intervene with preventive strategies. Within the epigenetic factors, diet- and nutrition-related factors play an important role in defining cancer susceptibility. Hormones and receptor systems under genetic and epigenetic control regulate the expression of genes responsible for cell growth and replication (*bottom right*). This simplified picture illustrates where much of present efforts are centered and where the greatest potential for future preventive strategies lies.

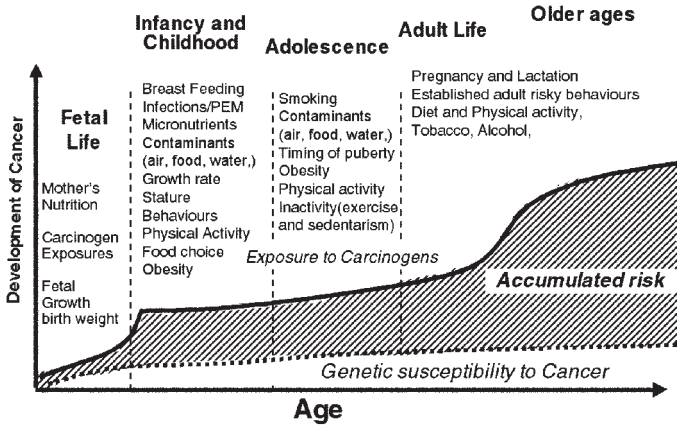

FIGURE 3 Graph of the life-course prevention of cancer illustrates how nutritional factors at various stages of the life course, starting from fetal life, may affect the development of cancer. The underlying genetic susceptibility to cancer is modified by diet, nutrition, and other carcinogenic agents in the environment, determining the accumulated risk for cancer. Cancer prevention should include actions at every stage of the life course; the greatest potential to combat cancer effectively is through reduction of cumulative risk.

possibly to increased cancer incidence in some parts of the world (17,20). Because most of the information presently available on early nutrition and adult cancer incidence is linked to obesity, we focus mainly on this risk condition in examining the life-course approach to cancer prevention (20).

Maternal nutrition and fetal growth. Healthy preconceptional weight decreases the risk of unfavorable outcomes of pregnancy mentioned above. Based on a meta-analysis of 61 studies published from 1970 to 1984, Kramer (63) reported that maternal underweight by itself increased the relative risk for fetal growth restriction almost 2-fold. Moreover, maternal short stature and low maternal weight for height or BMI both were associated with fetal growth restriction. In populations with a high prevalence of short stature, low maternal height accounts for a sizeable portion of infants with fetal growth restriction. Regardless of the cause of small maternal size, the deficit in maternal stature imposes limitations on the growth of the uterus, placenta, and fetus. Pregnant immature, underweight adolescents are at increased risk of bearing infants with fetal growth restriction and low birth weight. Young adolescent mothers who conceive close to their menarche are at especially high risk (64). Because a woman born at low birth weight is at increased risk for bearing infants of low birth weight, early pregnancy may have a long-term effect on rates of low birth weight (65). Women who are very thin or very short when they conceive are at increased risk for delivering an infant with fetal growth restriction. Epidemiological evidence suggests that the prevalence of a number of adult-onset diseases (obesity, hypertension, coronary heart disease, diabetes mellitus) is higher among adults who were small at birth or small at age 1 y. As previously indicated, postnatal weight gain of low-birth-weight infants also increases the risk for the metabolic syndrome, which has been considered to favor some types of cancers (66).

Maternal overweight and obesity also pose increased risks to mothers and offspring. Carey et al. (67) found that both high prepregnancy BMI (>25) and a weight gain of at least 5 kg in early adulthood are independent risk factors for obesity and gestational diabetes. The risk for gestational obesity and diabetes increased with greater weight gains between age 18 and ages 25 to 42 y, and it also was higher for nonwhite than for white women. These results suggest that avoiding substantial weight gain in the early adult years is an important strategy to reduce the risk of obesity and gestational diabetes—a condition that is associated with increased risk for perinatal morbidity (68) and perinatal mortality among obese women (69). Infants born of mothers who are overweight are more frequently macrosomic at birth and later in life are at increased risk of diabetes A life-course approach to weight management of mothers is needed—one that addresses balanced dietary intake and appropriate levels of physical activity beginning before adolescence and continuing throughout the reproductive years. The focus during pregnancy is on weight gain that is adequate without being excessive. For women who are already overweight or obese, careful weight management in the prenatal period and a modest weight loss in the postpartum period can have important health benefits and can be undertaken safely for mother and infant. The postpartum period, however, should not be relied on as the sole period in which to correct overweight or obesity before the next pregnancy (70).

Recommendations: Encourage adolescents and women of reproductive age to maintain a healthy BMI (18.5–24.9), because healthy weight before pregnancy decreases the risk of low birth weight and macrosomia. Increase the average age at first parity where pregnancies in adolescence and the accompanying low birth weight have a high prevalence. Assist women to gain a healthy amount of weight during pregnancy, then help them to achieve a healthy weight in the postpartum period.

Infant feeding and child growth. Normal infants gain a disproportionate amount of body fat in the first 6 to 8 mo of life; fat deposition slows from approximately the age of weaning onward. Children that become progressively and excessively fat at ages when other children are tending to show a decrease in fatness and BMI may have an increased risk for obesity. Normal children show a decrease in BMI after age 2 y, reaching a nadir at ages 3 to 5 y, then gain body fat and BMI; this has been termed the adiposity rebound. Children who have an early adiposity rebound have a significantly increased risk for overweight and obesity as children and persistent obesity into adulthood. Studies vary on the relation of overweight and obesity in infancy and their links to excess body weight in later childhood and adolescence (71).

Feeding practices including lack of breastfeeding and early introduction of solid foods have been reported to increase the risk of overweight and obesity in later life. Several recent large studies examined whether breastfeeding might have a protective influence on subsequent childhood obesity. Most studies suggest a protective effect of breastfeeding on obesity and on the risk of type 2 diabetes (72–74), but others argue that the apparent effect may be due to confounding with other factors such as social class, maternal fatness, maternal diabetes status, maternal reluctance to breastfeed, or infant birth weight (75). Koletzko and Von Kreis (76) studied >10,000 children in Bavaria and found that a significantly greater proportion of children who had been formula fed as infants were obese at school entry (age 5 or 6 y), compared to those who had been breastfed. The protective effect was dose dependent, with better protection against excess weight gain among children with the longest duration of breastfeeding as infants. However, the authors acknowledge the potential role of confounding factors, including social class, smoking during pregnancy, and general family dietary habits. Armstrong and Reilly's (77) study of 32,000 children age ~3.5 y found that obesity was significantly lower in breastfed children after adjustment for socioeconomic status, birth weight, and gender.

The mother's smoking behavior, BMI, and socioeconomic status also strongly influence the child's risk of overweight, but the differences between formula-fed and breastfed infants remain after controlling for these factors. The early introduction of solid foods can lead to excess energy intake by increasing the energy density of the diet. The duration of breastfeeding and the age of introduction of solid foods might thus influence the infant's regulation of energy intake and consequent weight gain, with earlier introduction of solid foods leading to more rapid weight gain in this age group than continued breastfeeding or, possibly, continued bottle feeding (78).

Persistence of fatness from childhood and adolescence to adulthood has been demonstrated in a number of studies, although the magnitude of the effect depends on the cutoffs used to define overweight or obesity, age of initial assessment, and length of follow-up. Correlations between childhood and adulthood adiposity are poor to moderate, on the order of 0.30, whereas correlations between ages 13 to 14 and 25 to 36 y vary from 0.46 to 0.91 for boys and 0.60 to 0.78 for girls (20). As the prevalence and degree of childhood obesity increase in populations, the strength of the correlations may also increase. Adolescence is one of the most vulnerable periods for the development of overweight and obesity and seems to be a period for entrainment of obesity-related morbidity. Increased morbidity and mortality seen in adulthood has been attributed to adolescent obesity directly rather than to the effects of adolescent obesity on adult weight (20). Although the mechanisms are unclear, fat distribution patterns established during adolescence may play a role. As pointed out earlier in this review, accelerated growth and fat gain at critical times have been significantly linked to the incidence of some cancers, such as premenopausal breast cancer and colon cancer.

Recommendations: Promote and support exclusive breastfeeding for 6 mo, with the introduction of complementary foods and continued breastfeeding thereafter—up to age 2 y or longer, as mutually desired by the mother and infant. Promote the appropriate introduction of safe, nutritionally adequate, and developmentally appropriate complementary foods. Ensure that the needs of infants and children at risk nutritionally are met, giving special attention to linear growth of preterm and low-birth-weight infants; prevent excess weight gain to decrease risk of obesity in later life. Monitor growth and avoid rapid weight gain at all stages of life; children should keep a healthy weight from early on. Create an environment that supports healthy food choices and promotes physical activity patterns concordant with a healthy lifestyle.

Early identification of children and adolescents at risk for obesity in preschool and school settings. Infants are 2 times more likely to become obese adults if one or both parents are obese than if both parents are at a healthy weight. This correlation is not explained completely by genetics. Shared environments and learned behaviors also contribute to it. Overweight that develops in childhood tends to persist into adulthood. For example, among children who were overweight at ages 10 to 15 y, >80% became obese by age 25 (79). Prevention of overweight during early childhood and adolescence is an important strategy for the prevention of adult obesity, especially because most adults who succeed in losing weight find it difficult to maintain weight loss over a long period.

A clearly defined method for assessing childhood obesity is needed to define those at risk; unfortunately, no single method is universally accepted. Definitions of overweight and obesity for children and adolescents are currently being reviewed because several alternative approaches have been proposed (80–82). Cultural issues are important for management and prevention. They may influence concepts of the attraction or risks associated with childhood obesity and thus willingness of families to comply with therapeutic advice. They also influence the lifestyle and self-esteem of obese individuals within a society. They can have a considerable effect on what should be included in dietary recommendations and on compliance with activity recommendations. The ease with which children can participate in activities away from home can be influenced by cultural norms and social integration of minority communities. Girls are probably affected particularly in relation to this latter point (83).

Screening of overweight and obese children can be conducted in schools (including preschool and daycare centers) (84) or healthcare organizations (such as polyclinics or health centers) (85). Depending on the definition of obesity, the population size, socioeconomic status of the country, and purpose of screening (e.g., for establishing prevalence and implementing intervention), each setting has its advantages and disadvantages

Recommendations: Identify children in schools and health centers with individual and or social risks for overweight and obesity early, establishing dietary and physical activity measures to prevent unhealthy weight gain. Monitor growth using appropriate standards, and take actions necessary to prevent stunting and avoid fatness in all children. Implement programs for the control and treatment of childhood obesity early to prevent present and future adverse consequences.

Conclusions

This review focuses on the paradigm of a life-course approach to the prevention of cancer, with an emphasis on the early, developmental events and influences. It suggests that the combination of specific dietary and environmental exposures and related metabolic and hormonal responses may confer increased risk for some types of cancer. Therefore, modification in early life of diet, nutritional status, body composition, growth, and physical activity patterns may help reduce cancer risk. Linking biomarker profiles that define cancer susceptibility with biomarkers of exposure to dietary components (nutrients and other bioactive chemicals) that modify cancer incidence may increase the efficacy and effectiveness of nutritional interventions. Nutrition and physical activity are key epigenetic factors affecting the timing and rate of growth and the endocrine responses that interact with genetic factors that define cancer risk. The life-course approach should be part of a strategy to enhance the effectiveness of interventions by focusing on reducing risk at critical windows in time and thus theoretically have the greatest effect on cancer incidence.

Given the strong evidence for nutrition (diet and physical activity) as a determinant of cancer risk, enabling the establishment of a healthful cancer-preventing diet and active living early in life is a public health priority. Respect for traditional cuisine and its combinations of foods is an essential component of ensuring a sustained healthful dietary condition in a society (86); the current trend toward free trade and globalization of food supplies acts against the conservation of dietary and food-preparation practices, as spelled out by the expert panel of the World Cancer Research Fund (42). A tolerance for food variety established in early life enables the selection of a varied diet, but it is not enough just to start on the right foods; the practices of consuming food of the appropriate quality and of maintaining an active life must be reinforced at all stages of the life course in order to lower cancer risk. Here lies the greatest potential for effective prevention.

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