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Is Timing Important? The Role of Diet and Lifestyle during Early Life on Colorectal Neoplasia

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Abstract

Purpose of the review—To summarize the current evidence on the most important dietary and lifestyle factors in colorectal carcinogenesis during different stages of a lifetime with special emphasis on studies investigating exposure during childhood, adolescence and young adulthood.

Recent findings—A number of studies showed that independent of adult obesity, higher body fatness during childhood, adolescence and young adulthood is associated with risk of colorectal cancer later in life. In one large cohort study, the Nurses' Health Study II, adherence to a western pattern diet during adolescence was associated with higher risk of advanced adenoma. The current evidence relating consumption of individual foods and nutrients as well as physical activity during early life to colorectal cancer is sparse and less consistent, at least in part due to limitations in study design, such as sample size, limited data on potential confounders or lack of a validated dietary assessment instrument.

Summary—As colorectal carcinogenesis is a long process and can take up to several decades to develop, early life risk factors may also be etiologically relevant. The recent rise in early-onset colorectal cancer incidence and mortality in the US, i.e., in individuals younger than 55 years at diagnosis, strongly supports that early life risk factors may influence colorectal carcinogenesis. Considering that the majority of colorectal cancers are preventable, there is an urgent need for well-designed investigations on the role of diet and lifestyle factors throughout the life course and risk of colorectal cancers.

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Conflict of Interest

Katharina Nimptsch and Kana Wu declare they have no conflict of interest.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Keywords

Diet; lifestyle; colorectal cancer; colorectal adenoma; life course; childhood; adolescence; young adulthood; overweight; obesity; red meat; processed meat; fiber; dairy; dietary pattern; physical activity

Introduction

Colorectal cancer (CRC) is a long process that requires decades to complete. Exposures during childhood and adolescence are likely to be critical because of the long subsequent lifetime at risk and because of enhanced susceptibility (1, 2). For example, puberty is associated with a physiological (and obesity unrelated) decrease in insulin sensitivity and concentration of growth factors, such as insulin-like growth factor 1 (IGF-1) have been reported to reach up to four times of that during adulthood (3–5). The recent rise in early-onset colorectal cancer incidence and mortality in the US, i.e., individuals younger than 55 years at diagnosis, provides additional support that early life risk factors may be operative in colorectal carcinogenesis (6, 7).

Almost all our knowledge of CRC is based on studies conducted using mid-to late life exposures, which may have missed etiologically relevant time periods. Data relating early-life exposures to colorectal cancers are scarce, because the influence of early life exposures on adult cancer risk is extremely difficult to investigate due to long follow-up, large sample size and the costs required. While there are ongoing efforts to pool data from birth cohorts or data from cohorts of children or adolescents (8), to date the main evidence relating diet and lifestyle factors during early life to risk of cancer in adulthood comes from historical cohort studies or ongoing cohort studies such as the Nurses' Health Study II (NHS II) (9, 10) or the NIH-AARP Diet and Health Study (11). In the cohort studies, early life exposure was assessed retrospectively, but participants were followed prospectively for incidence of cancers. Besides the ability to expedite research in this field, considerably lower cost and control for a variety of potential confounders, using existing resources from ongoing cohort studies also enables investigation of joint associations and whether observed associations for early-life exposures are independent of adult exposures.

In this brief review, we will provide an overview of the current knowledge on the association between body fatness, diet and physical activity during different stages of a lifetime and risk of colorectal neoplasia with special emphasis on studies investigating exposure during childhood, adolescence and young adulthood. We will summarize studies for both colorectal cancer and colorectal adenoma, which are established precursors for colorectal cancer and the preferred target for colonoscopy rather than cancer. Investigations on early life smoking or adult attained height (a marker for high exposure to growth factors in early life) and colorectal cancer risk are not included in this review, as those have been reported in detail elsewhere (e.g., (12, 13)).

Body fatness

Based on review of existing prospective studies, the most recent Continuous Update Project for colorectal cancer by the World Cancer Research Fund 2017 concluded that the evidence relating body fatness in general as well as abdominal fatness to colorectal cancer is “convincing” (14). Suggested underlying mechanisms for this association include hyperinsulinemia, insulin resistance and increased inflammation related to obesity (15, 16). This hypothesis is also supported by a growing number of molecular epidemiological studies showing that obesity-related biomarkers such as inflammatory markers, insulin, IGF-1 and adipokines such as adiponectin are associated with colorectal cancer risk (17–20).

The rising prevalence of obesity in children and adolescents poses a major public health problem in many westernized countries, because it is associated with the earlier onset of metabolic diseases such as insulin resistance, type 2 diabetes, high blood pressure and dyslipidemia (21). The impact of juvenile obesity on carcinogenesis is less well understood (2, 22). Because the positive association between obesity and colorectal cancer is at least partly mediated by high circulating insulin levels, initial steps in colorectal carcinogenesis may be influenced by alterations in basal insulin levels as have been observed in young obese (23, 24). A limited number of epidemiological studies investigated whether obesity during childhood, adolescence or young adulthood are associated with colorectal neoplasia later in life (Table 1).

Because body weight and height are standard measures and often obtained during routine medical examinations, several investigations have linked measured anthropometry data from children, adolescents and young adults to current registry data and examined the association between early life body fatness and risk of CRC after several decades of follow-up (25–31). The most recent investigation of this kind was performed in Sweden, where anthropometric data from the conscription assessment in late adolescence (mean age 18 years) was linked to cancer registry data in 239,658 men (29). Investigators found that compared with normal weight, an upper range of being overweight (body mass index (BMI) 27.5–<30 kg/m²) during late adolescence was associated with a 2-fold higher risk of colorectal cancer later in life, and obesity (BMI ≥ 30 kg/m²) was associated with a 2.4-fold higher risk. Interestingly, this study also found that inflammation during late adolescence, measured by high erythrocyte sedimentation rate, was positively associated with risk of colorectal cancer. In the largest study to date from Israel, BMI was measured in 1.1 million young male Israelis (16–19 years) during a medical board examination who were then followed for disease occurrence by linkage with a cancer registry (mean follow-up 17.6 years). Men with a high BMI (>85th percentile) during late adolescence/early adulthood had a 53% higher risk of later colon cancer, while no association with rectal cancer was observed (31). In the Harvard Alumni Health study, BMI was measured in male undergraduates (mean age 18 years) who were then followed for causes of death (average follow-up time of 56 years from university entry). In that study, no association between higher BMI during early adulthood and risk of death from colorectal cancer was observed (27). The association between adolescent BMI and colorectal cancer death in both men and women was investigated in Norway where BMI was measured in 226,678 adolescents as part of the Norwegian Health Survey and individuals were then followed for cause of death for an average of 35 years. Both men and

women who were in the highest BMI category (>85th percentile, in the US reference population) during adolescence had a two-fold higher risk of dying from colon cancer when compared to those in the 25th–74th percentile of BMI (25). While many registry-based investigations have the advantage that early life body fatness was directly measured (rather than calculated using self-reported weight and height from questionnaires), most studies lacked the ability to adjust for important potentially confounding factors and investigate obesity at different stages in life separately. Thus, observed associations could at least in part be due to residual confounding. Furthermore, the lack of adult exposure data limits the ability to distinguish whether observed associations for early life body fatness are independent of body fatness during adulthood because obesity in early life is one of the determinants for adult obesity (32).

The NHS II is a large cohort of 116,671 female registered nurses residing in the US who were between 25 and 42 years old at enrolment in 1989. On the 1989 baseline questionnaire NHS II participants recalled their body shape as an indicator of body fatness at ages 5, 10 and 20 years using a validated figure drawing with 9 consecutive body shapes (33, 34). Women who reported being overweight (body shape level 6 or higher) at age 5 years had a 44% higher risk of colorectal adenoma, which is a precursor of colorectal cancer (35), compared with women who were lean (body shape level 1) at that age. Observed associations were adjusted for potentially confounding factors and independent of adult BMI (36). In the corresponding analysis for body fatness at age 10 years a non-significant positive association was observed, while body fatness at age 20 years was not associated with later risk of colorectal adenoma. Using the same 9-level figure drawing, body fatness during early life was also recalled by participants of the two older parallel cohorts from the same group, the Nurses' Health Study (NHS) I, which included 121,700 female nurses residing in the US aged 35–55 years at baseline in 1976 and the Health Professionals Follow-up Study (HPFS), an older cohort of 51,529 US male health professionals aged 45–75 years at baseline in 1986. A higher risk of colorectal cancer was observed in women in the NHS I who reported higher body fatness (body shape level 5 or higher versus level 1) during childhood or adolescence. Positive associations between early life body fatness and colorectal cancer in the NHS I were independent of adult BMI (37). In contrast, early life body fatness was not significantly associated with risk of colorectal cancer later in life in the male HPFS cohort. In the Atherosclerosis Risk in Communities cohort, a prospective cohort including 13,901 men and women who were 45–64 years old at baseline (1987–1989), BMI in early adulthood (based on self-reported weight at age 25 years) was not associated with colorectal cancer incidence or mortality after adjusting for a variety of potential confounders including weight change from age 25 years to baseline (follow-up: 1987–1989 to 2006) (38).

Physical activity

Physical activity is considered an established risk factor for colorectal cancer (14). In a meta-analysis on the association between physical activity during adulthood and risk of colorectal cancer that included data from 52 epidemiological studies, a 24% lower risk of colorectal cancer was observed comparing the most active with the least active individuals across all studies, and the association was slightly stronger in case-control than in cohort studies (39). The inverse association was seen in both men and women. Similarly, in a meta-

analysis on physical activity and risk of colorectal adenoma, inverse associations were observed in both men and women (40). The hypothesized biological mechanisms through which higher physical activity may decrease the risk of colorectal neoplasia include reduction of bowel transit time resulting in shorter potential contact time for foodborne carcinogens, metabolic benefits resulting in lower levels of insulin and/or IGF-1, lower inflammation and modulation of immune function (39, 40). Despite the well-established association between physical activity during adulthood and lower risk of colorectal neoplasia, only few studies investigated the association between early life physical activity and risk of colorectal cancer or adenoma.

In 17, 148 men of the Harvard Alumni Study, physical activity was measured using participants' self-report on number of stairs climbed, blocks walked and sports play, in 1962 or 1966 and 15 years later in 1977. Participants were then followed until 1988. Neither physical activity reported in 1962/1966 nor physical activity in 1977 was associated with risk of colorectal cancer separately. However, participants who were physically active at both time points had a 50% lower risk of colon but not rectal cancer (41). Two case-control studies investigated the association between physical activity at ages 15–19 years and risk of colorectal cancer and observed inverse associations with higher occupational activity but not leisure time activity at that age (42, 43). The scarcity of studies precludes any conclusion regarding the role of early life physical activity in colorectal neoplasia, especially considering that the few available studies on the topic were limited in statistical power and physical activity measures were not validated previously.

Energy restriction

Evidence from data from northern Europe showed that individuals who were subject to severe energy restriction as children or adolescents during World War II had a lower risk of developing colorectal cancer later in life (1, 44), suggesting that diet during early life may play a role in colorectal cancer development. In the Netherlands Cohort Study on diet and cancer, participants who were exposed to famine during the “Hunger Winter” as adolescents exhibited a lower risk of CpG island methylation phenotype (CIMP)-high, but not CIMP-low colorectal cancers, than compared to those not exposed to severe famine during adolescence. The findings from that study indicate that adolescence may be a time period susceptible to epigenetic modulations by diet and lifestyle, which can increase risk of colorectal cancer risk later in life (45).

Red and processed meat

In 2015, a working group of the International Agency for Research on Cancer (IARC) concluded that processed meat is carcinogenic and unprocessed red meat probably carcinogenic to humans (46). This conclusion was largely based on the observed associations between red and processed meat intake during adulthood and risk of colorectal cancer. In a meta-analysis of 21 prospective cohort studies, dietary intake of red and processed meat during adulthood was significantly positively associated with colorectal cancer risk (47). In a dose-response analysis, a 17% higher risk of colorectal cancer was observed with each 100g increment of red meat and an 18% higher risk with each 50g

increment of processed meat intake. Positive associations between red and processed meat intake during adulthood and risk of colorectal adenoma have also been observed in a meta-analysis with consistent findings across studies (48). Red and processed meat may contribute to colorectal carcinogenesis through heterocyclic aromatic amines and related compounds that are formed during the cooking process as well as *N*-nitroso compounds (NOCs) that are formed endogenously from nitrate or nitrite, which are common additives in processed meats. In addition, heme iron, which is abundant in red meat, catalyzes the formation of NOCs and oxidizes lipids, and has therefore been suggested to play a role in colorectal carcinogenesis (49–51).

Few studies have investigated the association between meat intake during childhood or adolescence and risk of colorectal neoplasia later in life (Table 2). In the NIH-AARP Diet and Health Study, a large prospective cohort of 292,737 men and women aged 50–71 years at baseline 1995–1996, dietary intake at ages 12–13 years was assessed via a 37-item food frequency questionnaire retrospectively. In that study, no significant associations between red or processed meat intake during adolescence and risk of colon or rectal cancer were observed (11). In the NHS II, diet during high school (grades 9–12, ages 13–17 years) was assessed in about 45,000 nurses using a high school food frequency questionnaire that showed reasonable reproducibility and validity (52, 53). In an investigation relating adolescent diet to risk of colorectal adenoma, neither red meat nor processed meat were related to higher risk of colorectal adenoma later in life (9). Interestingly, high intake of poultry during adolescence was associated with lower risk of colorectal adenoma, independent of adult poultry intake. Furthermore, replacing a serving of adolescent total red meat (unprocessed red meat and processed red meat) with a serving of poultry or fish was associated with a lower risk of colorectal adenoma. While red and processed meat intake during adulthood is considered an established risk factor for colorectal neoplasia later in life, it is unclear why red or processed meat intake during adolescence was not associated with risk of colorectal adenoma in the NHS II. One possible explanation is that the median intake of red meat during high school in the NHS II participants was almost double of the median intake during adulthood and the number of nurses with low or no red meat intake during adolescence was low (reference category). However, it is also possible that red and processed meat may operate during different stages of carcinogenesis. In another NHS II investigation, using principal components analysis, two major dietary patterns during high school were identified, the prudent pattern, characterized by high intakes of vegetables, fruit, better quality grains, fish and poultry and the western pattern characterized by high intakes of desserts and sweets, red and processed meat, snack foods, fries and refined grains. In that study, the western dietary pattern during adolescence was associated with higher risk of rectal and advanced adenomas later in life (10). Besides red and processed meat, the western dietary pattern was also characterized by high intakes of foods high in added sugar (e.g., soda, sweets or desserts). Thus, further investigation into the role of fructose and sucrose during adolescence on colorectal neoplasia is warranted.

Fiber

Higher fiber intake has long been considered a protective factor in colorectal cancer development and the association between adult dietary fiber intake and colorectal cancer risk

has been examined in numerous epidemiological studies. The World Cancer Research Fund 2017 report on colorectal cancer concluded that the evidence relating higher intake of foods containing dietary fiber or whole grains to lower risk of colorectal cancer is probable (54). In a meta-analysis of 25 prospective investigations, each 10g increment of daily dietary fiber was associated with ten percent lower colorectal cancer risk (55). These results were also corroborated by another meta-analysis of case-control and cohort studies (56). Although the exact mechanisms are unclear, several plausible hypotheses have been suggested. These include decreased transit time, which reduces the contact time between carcinogens and the colorectal mucosa, reduction of secondary bile-acid production and short chain fatty-acid formation via fiber fermentation by gut microbiota (57, 58). We are aware of only one investigation of dietary fiber intake during adolescence and risk of colorectal cancer (Table 2). Interestingly, in the NIH-AARP Diet and Health retrospectively assessed dietary fiber intake during adolescence was associated with a higher risk of rectal cancer and a higher risk of colon cancer in women, independent of recent adult intake (11). Authors explained that food composition data for fiber was not available for the relevant time period and imputed data from the 1999 National Health and Nutrition Examination (NHANES), which may have introduced error. In addition, adolescent fiber intake in the NIH-AARP Diet and Health study was very low and it is possible that a risk-reducing threshold for fiber intake may not have been reached. In contrast, in the NHS II a prudent dietary pattern, characterized by high intakes of foods high in fiber such as fruits and vegetables and better quality grains was associated lower risk of rectal adenoma (10) (Table 2).

Dairy

There is substantial evidence from prospective investigations and from meta-analyses (59, 60) that higher dairy intake during adulthood is associated with lower risk of colorectal cancer. The most recent World Cancer Research Fund's Continuous Update Project on colorectal cancer 2017 concluded that the evidence relating higher consumption of dairy products and calcium supplements can decrease risk of colorectal cancer is "probable" (14). Postulated underlying mechanisms include binding of secondary bile-acids and ionized fatty acids by calcium, which can reduce cell proliferation and inflammation (61). One investigation on the association between dairy intake during early life and risk of colorectal cancer was conducted in the British Boyd Orr cohort, a study of 4,999 children born in the 1920s or 1930s, with a follow-up of up to 65 years. Dairy consumption during childhood was assessed through household food inventories, and a positive association between childhood dairy consumption and risk of colorectal cancer later in life was observed, although the analysis was based on a small number of cases (76 cases) (62). In the NIH-AARP study, higher milk intake during adolescence was associated with a lower risk of colon cancer, but these findings were substantially attenuated after taking adult dairy intake into account (63) (Table 2).

Conclusions

There is compelling evidence from numerous prospective studies that diet and lifestyle during adulthood are associated with risk of colorectal neoplasia, but little is known about the role of timing of exposure on colorectal carcinogenesis. Only a limited number of studies

have examined the role of early life body fatness on the development of colorectal neoplasia later in life. The majority of studies, including three large studies each comprising >32,000 participants, observed that higher body fatness during earlier stages of life may increase risk of colorectal neoplasia later in life. Two of these three studies were able to assess whether associations were independent of adult body fatness. Lack of information on adult body fatness may limit interpretation of the remaining studies. Potential differences in associations between early life body fatness and colorectal neoplasia by sex also warrants further consideration. Nonetheless, maintaining a healthy weight in children and adolescents remains the overarching goal to improve overall health and to lower risk of early-onset chronic diseases.

While higher red and processed meat intake during adulthood is considered an established risk factor for colorectal cancer, the lack of association between early life red and processed meat intake in two large cohort studies highlight the importance of considering timing of exposure when examining these associations. Evidence concerning intake of other foods or nutrients or physical activity during early life is limited and inconsistent, but warrants further investigation. Using existing resources from large cohort studies to collect and validate early life diet and lifestyle data (particularly in younger cohort participants) can expedite research and considerably lower costs to study these associations and consequently inform cancer prevention strategies.

The recent rise in early-onset colorectal cancer incidence and mortality in the US, i.e., in individuals younger than 55 years at diagnosis, strongly supports that early life risk factors may influence colorectal carcinogenesis. Thus, investigation of early life exposures may also help to lower incidence and mortality of these early-onset cases, which current screening recommendation do not address.

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Summary of findings from studies that investigated body fatness during childhood, adolescence or young adulthood and risk of colorectal neoplasia

Table 1

Reference Country (Study name)	Study participants	Exposure assessment (age at assessment)	Follow-up	Outcome (number of cases)	Analytical comparison Relative risk (95% CI)	Covariates
Kantor et al. 2016 (29) Sweden	239,658 men	Measured BMI in late adolescence (mean age 18 years)	35 years; 1969–1976 to 2010	Colorectal cancer (885) in men, 808 in women)	Compared with normal weight (BMI 18.5–<25 kg/m ²): upper overweight (BMI 27.5–<30 kg/m ²) 2.08 (1.40, 3.07) obesity (BMI ≥30 kg/m ²) 2.38 (1.51, 3.76)	Age at conscription, household crowding, health status, systolic and diastolic blood pressure, muscular strength, physical working capacity, cognitive function, erythrocyte volume fraction, erythrocyte sedimentation rate
Zhang et al. 2015 (37) USA (Health Professionals Follow-up Study, Nurses' Health Study)	75,238 women, 34,533 men	Recalled body shape at ages 5, 10 and 20 years (using a 9-level pictogram: 1 = most lean body shape, 9 = most overweight body shape)	22 years	Colorectal cancer (2,100; 1,292 in men, 808 in women)	Body shape level 5 or higher versus 1 in childhood (average of body shape at age 5 and 10 years): men 1.04 (0.82, 1.31) women 1.28 (1.04, 1.58) in adolescence (average of body shape at age 10 and 20 years): men 0.98 (0.75, 1.27) women 1.27 (1.01, 1.60)	Age, height, smoking before age 30, family history of colorectal cancer, history of sigmoidoscopy/endoscopy, current physical activity, regular aspirin use, <u>adult BMI</u>
Han et al. 2014 (38) USA (Atherosclerosis Risk in Communities Study)	13,901 men and women	Self-reported weight at age 25 years	1987–1989 to 2006 (incidence) or 2009 (mortality)	Colorectal cancer incidence (147) and mortality (41)	Per 5 kg/m ² increase in BMI colorectal cancer incidence women 1.04 (0.84, 1.35) men 1.21 (0.94, 1.55) colorectal cancer mortality women 1.02 (0.61, 1.70) men 1.41 (0.95, 2.11)	Race, center, age, education, height, smoking status at age 25, cigarette smoking status, alcohol consumption, physical activity at baseline, weight change percentage from age 25 to baseline
Gray et al. 2012 (27) USA (Harvard Alumni Health Study)	19,593 men	Measured BMI in early adulthood (mean age 18.4 years)	56.5 years; 1914–1952 to 1998	Mortality from colorectal (270) and colon (228) cancer	Per standard deviation (2.56 kg/m ²) increase in BMI colorectal 1.09 (0.93, 1.27) colon 1.11 (0.94, 1.31)	Age, cigarette smoking status, physical activity at college entry, <u>BMI in 1962/1966</u>
Levi et al. 2011 (31) Israel	1.1 million men	Measured BMI in late adolescence/early adulthood (16–19 years)	17.6 years; 1976–2005 to 2006	Colon (545) and rectal (193) cancer	BMI >85 th percentile versus 85 th percentile colon 1.53 (1.17, 2.00) rectum 1.09 (0.68, 1.73)	Year of birth, age at BMI assessment, country of origin, residence, immigration status, socioeconomic status, height
Nimptsch et al. 2011 (36) USA (Nurses' Health Study II)	32,707 women with at least one lower bowel endoscopy during follow-up, age 25–42 y at baseline 1989	Recalled body shape at ages 5, 10 and 20 years (using a 9-level pictogram: 1 = most lean body shape, 9 = most overweight body shape); pictogram	1991–2005	Colorectal adenoma (2,327)	Body shape level 6 or higher versus 1 at age 5: 1.40 (1.01–1.94) at age 10: 1.17 (0.90–1.52) at age 20: 0.95 (0.68–1.34)	Age, family history of colorectal cancer, time period of endoscopy, number of endoscopies during the study period, reason for most recent endoscopy, height, pack-years of smoking, physical

Reference Country (Study name)	Study participants	Exposure assessment (age at assessment)	Follow- up	Outcome (number of cases)	Analytical comparison Relative risk (95% CI)	Covariates
		included in baseline questionnaire in 1989				activity, aspirin use, alcohol intake, adult intake of red meat, processed meat, folate, calcium, adult BMI
Burton 2010 (26) UK	12,206 men and women	Measured BMI (mean age 20 years)	47.5 years; 1948– 1968 to 2009	Colorectal cancer (125; 110 in men, 15 in women)	BMI 25 versus 19–22.9 kg/m ² men 1.25 (0.60–2.61) women 1.23 (0.15–10.07)	Smoking, father's social class, height, age at menarche, sex
Bjorge et al. 2008 (25) Norway	226,678 men and women	Measured BMI in adolescence (14–19 years)	35 years; 1963–1975 to 2005	Mortality from colon cancer (205; 97 in men, 108 in women)	BMI 85th versus 25th–74th percentile (of reference population) men 2.1 (1.1–4.1) women 2.0 (1.2–3.5)	Age at measurement, year of birth
Jeffreys 2004 (28) UK (Boyd Orr Cohort)	2,347 men and women (from 992 families)	Measured BMI in childhood (2–14 years)	50 years; 1937–39 till 2003	Colorectal cancer (38)	Highest versus lowest quartile (BMI z scores) 1.36 (0.57– 3.24)	Age at the time of BMI measurement, sex
Must 1992 (64) USA (Harvard Growth Study)	503 men and women	Measured BMI at age 13–18 years	55 years; 1922–1935 to 1988	Mortality from colorectal cancer (10; 6 in men, 4 in women)	BMI 75th versus 25th–50th percentile (of reference population) men 9.1 (1.1–77.5) women 1.0 (0.1–7.0)	
Le Marchand 1992 (30) USA	52,539 men	Recorded BMI at age 15–29 years	1942 to 1972–86	Colon (421) and rectum (316) cancer	Highest versus lowest BMI tertile colon cancer 1.6 (1.2– 2.1) rectal cancer 0.7 (0.6–1.4)	Matching on month/year of birth and ethnicity; adjusted for socioeconomic status in 1972

Table 2

Early life diet and risk of colorectal neoplasia

Reference Country (Study name)	Study participants	Exposure assessment	Follow-up	Outcome (number of cases)	Analytical comparison Relative risk (95% CI)	Covariates
Ruder 2011 USA (NIH-AARP cohort)(63)	292,797 men and women, age 50–71 y at baseline in 1995–1996	37-item FFQs about diet at ages 12–13 y and 10 y prior to baseline; assessment at baseline in 1995–96	1995–1996 to 2006	Colon (2794) and rectal (979) cancer	Highest versus lowest quintile of red or processed meat intake during adolescence Colon 1.09 (0.93, 1.28) Rectum 1.08 (0.83, 1.40) Highest versus lowest quintile of fiber intake during adolescence Colon 1.05 (0.93, 1.19) Rectum 1.29 (1.04, 1.60) Highest versus lowest quintile of milk intake during adolescence Colon 0.92 (0.78, 1.10) Rectum 0.99 (0.73, 1.34)	Adjusted for energy intake at ages 12–13 y, energy intake in recent adulthood, nutrient or food of interest in recent adulthood, age at completion of risk-factor questionnaire, sex, BMI, race, education, physical activity, alcohol consumption, smoking, use of aspirin and ibuprofen, use of hormone replacement therapy, and self-report of a first-degree relative with a history of colon cancer
Van der Pols 2007 United Kingdom (Boyd Orr Cohort)(62)	4,383 men and women, who were children at the time household intake was estimated; (mean age: 8 y; interquartile range: 4–11 y in 1937–1939	Study of family food consumption, assessed from 7-d household food inventories; Per capita household intake estimates for dairy products and calcium were used as proxy for individual intake	1948–2005	Colorectal cancer	Highest versus lowest quartile of childhood dairy intake 2.90 (1.26, 6.65)	Adjusted for age, sex, and energy and fruit intakes
Nimptsch 2013 USA (Nurses' Health Study II)(65)	19,771 women with at least one lower bowel endoscopy during follow-up, age 25–42 y at baseline 1989	124-item validated FFQ about diet during high school (grades 9–12, ages 13–17 years), completed in 1998 at age 34–49 y	1998–2007	Colorectal adenoma (1,494)	OR highest (> 200 g/day) versus lowest (<75 g/day) category of red or processed meat intake during adolescence, 1.04 (0.81,1.35)	Multivariable adjusted for age, family history of colorectal cancer, time period of endoscopy, number of reported endoscopies during the study period, endoscopy prior to study period, reason for most recent endoscopy, height, BMI at age 18, packyears of smoking, current physical activity, physical activity during 9th–12th grade, aspirin use, high school energy intake, current cumulative average alcohol intake, adult energy and red or processed meat intake
Nimptsch 2014 USA (Nurses' Health Study II)(10)	17,221 women with at least one lower bowel endoscopy during follow-up, age 25–42 y at baseline 1989	124-item validated FFQ about diet during high school (grades 9–12, ages 13–17 years), completed in 1998 at age 34–49 y	1998–2007	Colorectal adenoma (1,299)	Highest versus lowest quintile of dietary pattern "prudent" pattern during adolescence, characterized by high consumption of vegetables, fruit and fish Colon 0.89 (0.71,1.11) Rectum 0.45 (0.27,0.75) "Western" pattern during adolescence,	Age, height, family history of colorectal cancer, physical activity during 9th–12th grade, pack-years of smoking before age 20 years, high school total calories, current body mass index, pack-years of smoking, current physical activity, aspirin use, time period of endoscopy, at least 2 endoscopies during the study period,

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Reference Country (Study name)	Study participants	Exposure assessment	Follow- up	Outcome (number of cases)	Analytical comparison Relative risk (95% CI)	Covariates
					characterized by high consumption of desserts and sweets, snack foods and red and processed meat Colon 1.05 (0.85, 1.30) Rectum 1.78 (1.12,2.85)	endoscopy prior to 1998, reason for most recent endoscopy, current cumulative average alcohol intake, adult total calories and respective adult dietary pattern