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Research Article

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Early Life Body Fatness and Risk of Colorectal Cancer in U.S. Women and Men—Results from Two Large Cohort Studies

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Abstract

Background: The association between body fatness before adulthood and later risk of colorectal cancer remains unclear. We hypothesized that, independent of adult body fatness, early life body fatness would be associated with a higher risk of developing colorectal cancer.

Methods: We assessed body fatness during childhood and adolescence using a validated 9-level somatotype and inquired body weight in young adulthood in the Nurses' Health Study and Health Professionals Follow-up Study. We used the Cox proportional hazard regression modeling to estimate relative risks [RR, 95% confidence intervals (CI)] adjusting for adult body mass index (BMI) and other known colorectal cancer risk factors.

Results: We identified 2,100 incident colorectal cancer cases (1,292 in women and 808 in men) during 22 years of follow-up. Among women, the RR (95% CI) for childhood body fatness of level 5 or higher versus level 1 was 1.28 (1.04–1.58; P_{trend} = 0.08) and for adolescent body fatness, it was 1.27 (1.01–1.60; P_{trend} = 0.23). The corresponding RRs for men were 1.04 (0.82–1.31; P_{trend} = 0.48) and 0.98 (0.75–1.27; P_{trend} = 0.20), respectively. Results were generally similar across anatomic subsites within the colorectum. In addition, the RRs comparing BMI categories ≥27.5 to <19 kg/m^2 were 1.44 (1.06–1.95, at age 18; P_{trend} = 0.009) for women and 1.18 (0.84–1.65, at age 21; P_{trend} = 0.57) for men.

Conclusion: Increased body fatness in early life, independent of adult obesity, might be a risk factor for colorectal cancer in women, but we observed a weaker association in men.

Impact: Our findings support the growing evidence that early life body fatness affects the risk of colorectal cancer many decades later. *Cancer Epidemiol Biomarkers Prev; 24(4); 690–7. ©2015 AACR.*

Introduction

Despite the increased implementation of endoscopy screening and improved treatment, colorectal cancer remains the third most incident and fatal cancer in both women and men in the United States (1). About 1 in 18 individuals will develop colorectal cancer over their lifetime and approximately 40% will die within 5 years of diagnosis (1). As shown in recent meta-analyses (2–4), being overweight or obese during adulthood is associated with an increased risk of colorectal cancer in both women and men, although stronger associations have been observed in men. The exact mechanisms underlying these observations are not fully understood, but insulin resistance, hyperinsulinemia, as well as alterations in sex steroids, insulin-like growth factors (IGF), and adipokines may be involved (5–8).

In contrast to the well-documented positive associations between overweight/obesity in adulthood and colorectal cancer risk, the potential effect of body fatness during childhood, adolescence, and young adulthood remains unclear. In fact, the long latency for colorectal cancer development suggests that certain exposures might have occurred in the distant past. It is plausible that childhood and adolescence represents a critical window during which adiposity influences later cancer risk (9). Increased body fatness in childhood and adolescent girls has been associated with an array of metabolic consequences, including higher basal insulin levels (10, 11), and thus may influence cancer risk through insulin resistance pathways or hyperinsulinemia. To date, a limited number of studies have evaluated the associations between early life body fatness and colorectal cancer risk and results have been equivocal (12–22).

We hypothesized that higher early life body fatness is independently associated with an increased risk of incident colorectal cancer in later life. To test this hypothesis, we conducted a study using early life anthropometric data collected from two large, prospective cohorts, the Nurses' Health Study (women; refs. 23,

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24) and the Health Professionals Follow-up Study (men; refs. 22). In this study, we extend our previous findings (19, 22) on body fatness in young adulthood (age 18 in women and age 21 in men) by including approximately three times as many years of follow-up and incorporating novel data on body fatness in childhood and adolescence.

Materials and Methods

Study population

The Nurses' Health Study (NHS; refs. 23, 24) was established in 1976, when 121,700 married female registered nurses of ages 30 to 55 years residing in 11 states in the United States completed and returned a self-administered questionnaire. The Health Professionals Follow-up Study (HPFS; ref. 22) is an ongoing cohort study of 51,529 U.S. male professionals who were of ages 40 to 75 years at baseline in 1986. Questionnaires have been mailed to participants in both cohorts every 2 years since baseline to collect updated information on demographics, lifestyle factors, medical history, and disease outcomes. The follow-up rate has been greater than 90% in both studies. The Institutional Review Board at the Brigham and Women's Hospital and Harvard School Public Health (Boston, MA) approved the studies. As approved by the committee, return of the questionnaires was considered to imply informed consent. In 1988, a total of 10,361 women and 51,529 men answered the questionnaire containing information on early life body fatness (see below sections), thus 1988 was our baseline year for our analysis. We excluded participants with a history of cancer at baseline (except nonmelanoma skin cancer, $n = 7{,}954$ for women, 2,803 for men), with ulcerative colitis ($n = 1{,}214$ for women, 584 for men), and with missing information on early life body fatness ($n = 19{,}163$ for women, 13,609 for men). The included participants were comparable with the overall cohorts with regard to major risk factors for colorectal cancer. The analytic cohort included 75,238 women and 34,533 men consisting of 2,272,716 person-years through 2010.

Assessment of early life body fatness

In 1988, participant in both cohorts were requested to choose one of nine pictorial body diagrams (somatotypes) developed by Stunkard and colleagues (25) that best depicted her or his body fatness at ages 5, 10, 20, 30, and 40 years and at their current age. Level 1 represents the most lean and level 9 represents the most overweight (Fig. 1). The validity of this measure of body fatness in early life was assessed by Must and colleagues (26) among 181 participants in the Third Harvard Growth Study. Participants between ages 71 and 76 years were asked to recall their body fatness at ages 5, 10, 15, and 20 years, using the same nine-level somatotypes. Pearson correlation coefficients between recalled body fatness during early life using this somatotype and measured body mass index (BMI) at approximately the recalled ages were 0.60 for age 5 years, 0.65 for age 10 years, and 0.66 for age 20 years in women (26). The corresponding Pearson correlation coefficients were 0.36, 0.66, and 0.53, respectively in men (26). In addition, we obtained self-reported body weight at age 18 years in 1980 in the NHS and body weight at age 21 years in 1986 in the HPFS. The validity of this type of question was evaluated in a similar cohort of women, the NHS II cohort and has been used in other studies (27, 28). The correlation for recalled weight versus college or nursing school records was 0.87 for weight at the age of 18 years.

Assessment of other covariates

We used validated food frequency questionnaires (FFQ) to obtain information on usual dietary intake over the past year in both cohorts (29, 30). The baseline and biennial questionnaires, included questions about colorectal cancer risk factors including height, adult body weight, physical activity (METs-h/wk), cigarette smoking, sigmoidoscopy/endoscopy screening, family history of colorectal cancer, and aspirin use. In women, information on menopausal status and postmenopausal hormone use was also obtained at baseline and on the subsequent follow-up questionnaires.

Identification of colorectal cancer cases

Cancer and other disease outcomes have been reported by the participants in each cohort on the biennial questionnaires. Researchers received permission from study participants to obtain medical records and pathologic reports on colorectal cancer and, while blinded to exposure information, abstract the information on anatomic location, stage, and histologic type of the cancer. For deceased participants with known or suspected cancer for which we have not been able to obtain medical records, we contacted the state tumor registry to confirm and classify the cancer. Colorectal cancer (carcinoma) was defined according to the International Classification of Diseases, Ninth Revision [ICD-9] (31). Colon cancer (ICD-9 codes 153.0–153.4, 153.6–153.9) was further classified into proximal colon cancer (neoplasms from the cecum to the splenic flexure; ICD-9 codes 153.0, 153.1, 153.4, 153.6, 153.7) and distal colon cancers (neoplasms in the descending

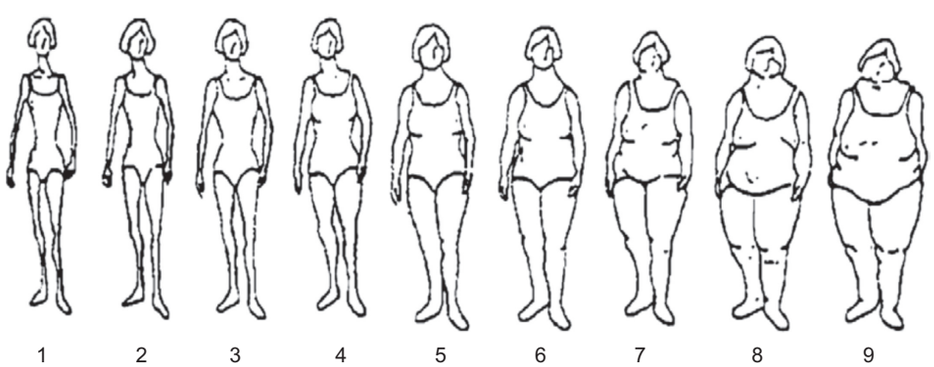

Figure 1.
Figure drawing used to assess body fatness at ages 5, 10, and 20 years in the NHS (1988). This figure was reproduced from Stunkard et al. (ref. 25; with permission from Lippincott Williams & Wilkins, Philadelphia, PA).

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[153.2] and sigmoid [153.3] colon). Rectal cancer (ICD-9 codes 154.0 or 154.1) was defined as that occurring in the rectosigmoid or rectum (31). Deaths (>98%) were identified from state vital statistics records, the National Death Index (32), reported by the families, and the postal system. Cause of death has been identified from death certificates or review of medical records.

Statistical analyses

We calculated person-time for each participant from the date of baseline questionnaire return to the date of death, colorectal cancer diagnosis, or the end of follow-up (May 31, 2010, for the NHS; January 31, 2010, for the HPFS), whichever occurred first. We used a Cox proportional hazards regression model (33) to calculate hazard ratios as an estimate of relative risks (RR) and 95% confidence intervals (95% CI) and adjusted simultaneously for age (in months) and year of questionnaire return. We observed no violation of the proportional hazard assumption based on the likelihood ratio test that compared the model with and without the interaction terms between somatotype variables and age or follow-up time. Given the reported apparent gender difference in the association between adult BMI and colorectal cancer risk (2–4), we tested our *a priori* hypothesis by evaluating associations with early life body fatness in women and men separately. We then tested for heterogeneity by sex using a random-effects model (34, 35).

Consistent with previous studies from the same cohort (28, 36), in our primary analyses, we defined childhood body fatness as the average of reported somatotype at ages 5 and 10 years and defined adolescent body fatness as the average of the reported somatotypes at ages 10 and 20 years. Because of a low number of cases in the categories greater than level 5, we collapsed the upper categories. We therefore categorized the child and adolescent body fatness as: 1 (reference group), 2–< 3, 3–< 4, 4–< 5, and 5+. In secondary analyses, we evaluated the associations with the reported somatotype at ages 5, 10, and 20 years, respectively. Consistent with a prior analysis in the same cohort (37), young adulthood BMI (age 18 years in women, age 21 years in men) was categorized as <19 (reference group), 19–<20.4, 20.4–<21.9, 21.9–<24.9, 24.9–<27.5, and ≥27.5 kg/m^2. We have further used World Health Organization (WHO) definitions for overweight and obesity for these analyses. Specifically, young adulthood BMI (age 18 years in women, age 21 years in men) was additionally categorized as <18.5 (reference group), 18.5–<23.0, 23.0–<25.0, 25.0–<27.5, 27.5–<30, and ≥30.0 kg/m^2. For this analysis, we excluded participants with extreme values in young adulthood (<15 or >45 kg/m^2). To test for linear trend, we used continuous variables of body fatness at young adulthood and somatotype as an ordinal score variable.

In addition to age, we adjusted for established nondietary and dietary risk factors in the multivariate models. To assess the independent association of early life body fatness, we further adjusted for biennially updated adult BMI. Additional adjustment for waist circumference, waist:hip ratio, and weight change between young adulthood and baseline did not appreciably change the results and were not included in final models.

Given the previous studies suggested that some specific factors may modify the associations between early life body fatness and colorectal cancer risk (15, 21, 38), we conducted stratified analysis by birth weight (<7, ≥7 pounds), height (<1.65, ≥1.65 m in women; <1.78, ≥1.78 m in men), adult BMI (<25, ≥25 kg/m^2), adult physical activity (<9, ≥9 MET-h/wk), and family history of colorectal cancer (no, yes), as well as menopausal status (pre-, postmenopausal, women only). We constructed the product term between early life body fatness (ordinal variables) and these dichotomized variables and tested whether β-coefficients of the cross-product terms were statistically significant using a Wald test. We conducted all analyses using the SAS software (SAS Institute, Inc., Version 9.2). All statistical analyses were two-sided with a P value less than 0.05 indicating statistical significance.

Results

We documented a total of 2,100 incident colorectal adenocarcinoma cases (1,292 in women and 808 in men) in these two cohorts during 22 years of follow-up. Table 1 shows the selected demographic, lifestyle characteristics, and potential confounding factors across the levels of childhood and adolescent body fatness in each cohort. The mean age at baseline was 55 years in women and 56 years in men. Individuals with higher body fatness in childhood and adolescence were slightly younger at baseline than those who were leaner (somatotype ≥ 5 vs. 1). Also, they were less physically active (in women but not in men). Smoking was more prevalent among individuals who had greater body fatness in childhood and adolescence. In addition, young adult BMI and adult BMI were positively associated with childhood somatotype and adolescent somatotype in both women and men, but especially so for women. Other baseline characteristics were comparable across the childhood and adolescent somatotype categories (Table 1). We further examined the distribution of adult waist circumference and waist:hip ratio by categories of somatotype at childhood and adolescence (Supplementary Table S1). In contrast to the expected positive correlation between higher body fatness in childhood and adolescence and higher BMI at young adulthood and adulthood, waist circumference and waist:hip ratio were roughly comparable across the categories of body fatness as measured by somatotype.

Comparing overweight girls (body shape level 5 or higher) to those who were most lean (body shape level 1), the multivariable RRs (MVRRs; 95% CIs) were 1.28 (1.04–1.58; $P_{trend} = 0.08$) for childhood body fatness, and 1.27 (1.01–1.60; $P_{trend} = 0.23$) for adolescent body fatness (Table 2). A similar pattern was seen when we conducted sensitivity analyses of somatotype at ages 5 and 10 years separately. For example, the MVRRs related to body fatness (body shape level 5 or higher vs. level 1) were 1.23 (95% CI, 1.00–1.50; $P_{trend} = 0.12$) for age at 5 years, and 1.15 (95% CI, 0.96–1.39; $P_{trend} = 0.14$) for age at 10 years in women. These results were not appreciably changed upon mutual adjustment for the somatotype at different ages (data not shown). Overall results were null in men (Table 2). Furthermore, results did not vary substantially by anatomic subsites of diagnosed colorectal cancer for both men and women (i.e., proximal colon, distal colon, and rectum; Supplementary Table S2).

Increased body fatness in young adulthood also was associated with risk of colorectal cancer in women. The MVRRs (95% CIs) comparing BMI ≥ 27.5 to <19 kg/m^2 were 1.44 (1.06–1.95; $P_{trend} = 0.009$, at age 18 years) in women and 1.18 (0.84–1.65; $P_{trend} = 0.57$, at age 21 years) for men (Table 3). There was no evidence of statistical heterogeneity by gender ($P_{heterogeneity} = 0.39$). No clear pattern was seen in additional analyses by subsites, although slightly stronger associations were noted for the distal colon cancer and rectal cancer in women (Supplementary Table S3).

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Table 1. Baseline (1988) age-adjusted characteristics of participants by categories of somatotype at childhood and adolescence in the NHS and the HPFS

	Women (NHS)				Men (HPFS)			
	Somatotype at childhood[d]		Somatotype at adolescence[e]		Somatotype at childhood[d]		Somatotype at adolescence[e]	
	Somatotype 1 (n = 29,808)	Somatotype 5+ (n = 5,303)	Somatotype 1 (n = 19,839)	Somatotype 5+ (n = 4,477)	Somatotype 1 (n = 12,632)	Somatotype 5+ (n = 4,301)	Somatotype 1 (n = 6,361)	Somatotype 5+ (n = 4,100)
Age, y	55.7 (7.0)	54.2 (7.0)	55.7 (6.9)	54.4 (7.1)	58.0 (9.4)	53.9 (9.3)	58.1 (9.2)	53.4 (9.1)
Young adult BMI[a], kg/m^2	18.3 (6.1)	22.4 (7.9)	17.6 (5.8)	23.8 (8.5)	23.0 (3.6)	23.4 (3.6)	22.8 (3.6)	23.4 (3.7)
Adult BMI in 1988, kg/m^2	23.8 (3.7)	27.0 (5.5)	23.1 (3.2)	28.2 (5.9)	25.0 (2.8)	26.7 (3.7)	24.4 (2.6)	27.0 (3.9)
Adult physical activity, MET-h/week[b]	15.0 (19.6)	14.5 (18.2)	15.0 (19.6)	14.0 (17.6)	23.9 (27.1)	26.3 (27.9)	23.0 (25.0)	25.9 (29.0)
Regular aspirin use (2 or more tablets/wk), %	61	63	61	62	42	41	41	43
Past smoking, %	36	40	35	41	43	47	45	48
Current smoking, %	18	24	18	22	8	9	8	9
Multivitamin use[c], %	38	38	38	38	40	40	40	40
Alcohol, g/d	6.3 (9.7)	6.3 (9.8)	6.4 (9.7)	5.5 (9.2)	11.6 (15.5)	11.4 (15.3)	11.6 (15.5)	11.1 (15.3)
Total calcium intake, μg/d	872 (327)	901 (332)	867 (321)	912 (341)	886 (421)	900 (430)	880 (418)	908 (437)
Red meat, servings/wk	2.2 (1.4)	2.2 (1.4)	2.3 (1.5)	2.1 (1.4)	1.8 (1.6)	1.7 (1.7)	1.9 (1.6)	1.7 (1.7)
Processed meat, servings/wk	1.0 (1.3)	1.0 (1.3)	1.1 (1.3)	1.0 (1.3)	1.3 (1.9)	1.2 (1.8)	1.3 (1.9)	1.2 (1.8)
Postmenopausal status, %	73	73	73	73	—	—	—	—
Postmenopausal hormone (PMH) use, %	38	35	39	34	—	—	—	—

NOTE: Values are means (SD) or percentages and are standardized to the age distribution of the study population except for the age variable.

[a]BMI was calculated as weight in kilograms divided by the square of height in meters; BMI at age 18 (NHS) or age 21 (HPFS).

[b]Hours of metabolic equivalent tasks.

[c]Dietary intakes were estimated with food-frequency questionnaire in 1986 except for multivitamin use from the 1988 questionnaire in each cohort.

[d]Average of somatotype at ages 5 and 10 years based on 9-level pictogram.

[e]Average of somatotype at ages 10 and 20 years based on 9-level pictogram.

We further conducted joint analyses by birth weight, height, adulthood BMI, physical activity, family history of colorectal cancer, and menopausal status. Although most P values for interaction were not statistically significant, we observed slightly stronger associations among individuals who were both heavier in early life and later life, as well as among women with tall stature (Table 4). The associations did not vary by other factors (all other P values for interactions ≥ 0.10).

Discussion

Using data from two large prospective studies, we found that for women, increased body fatness in childhood, adolescence, and young adulthood was significantly associated with an increased risk of colorectal cancer; importantly, this association was independent of adult BMI. In contrast, we observed little evidence for an association in men.

Numerous studies, as summarized in recent comprehensive meta-analyses (2–4), have reported significant positive associations between body fatness (generally measured using BMI) during adulthood and risk of colorectal cancer. For example, a meta-analysis of 56 observational studies including 93,812 colorectal cancer cases found that obesity (BMI $\geq$ 30 vs. <23 kg/m^2) was associated with an increased risk of colorectal cancer in both women (RR, 1.25; 95% CI, 1.14–1.37) and men (RR, 1.53; 95% CI, 1.44–1.62; ref. 4). In contrast, fewer studies have examined the associations between early life body fatness and colorectal cancer risk (12–22). Among the 11 studies we identified, seven studies (15–21) indicated positive associations between increased body fatness in adolescence and young adulthood (ages range, 13–29 years) and colorectal cancer risk (RRs ranged from 1.3 to 2.4). In addition, two studies (39, 40) observed an approximately 2-fold increase in colorectal cancer mortality related to BMI greater than 85th percentile measured during adolescence, though two others reported null associations (13, 41). We only identified one study that evaluated childhood body fatness (mean age 8 years) in relation to colorectal cancer risk (12). Jeffery and colleagues (12) observed a nonsignificant 36% (RR, 1.36; 95% CI, 0.70–3.24) increase in risk of colorectal cancer comparing top with bottom quartile of body fatness in childhood, but the sample size was small (n = 38 cases, women and men combined). Taken together, the current literature in aggregate appears to support a role of early life body fatness in colorectal carcinogenesis. Our findings of significant positive association with larger body fatness in early life in women are in line with the current body of knowledge.

It is challenging to disentangle the independent associations between early life obesity and adult obesity because childhood and adolescence obesity often tracks to adulthood (42). In our analyses, the positive associations with increased body fatness in early life in women persisted after adjustment for adult BMI. Whereas previous studies on early life body fatness and colorectal cancer including those in men have reported positive associations (15–18, 20, 21), the positive association we observed in women is consistent with findings from a study conducted by Russo and colleagues (20) on colorectal cancer and two studies (38, 43) on adenomas. Although chance finding cannot be totally excluded, overweight boys and girls are more likely to show insulin resistance in late life (11). Insulin resistance is linked to hyperinsulinemia, which is associated with higher bioactive or free IGF-1 levels (5–7). Both the insulin and IGF axis have generally been

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Table 2. Multivariable RRs of colorectal cancer according to body fatness at childhood and adolescence in the NHS and the HPFS (1988–2010)

	Somatotype 1	Somatotype 2–<3	Somatotype 3–<4	Somatotype 4–<5	Somatotype 5+	P_{trend}[c]
Women (NHS)						
Cases, *n*	512	309	215	144	112	
Body fatness at childhood, MV[a]	1 (Reference)	1.11 (0.96–1.28)	1.03 (0.87–1.20)	1.10 (0.91–1.31)	1.32 (1.08–1.63)	0.03
Body fatness at childhood, MV+BMI[b]	1 (Reference)	1.10 (0.96–1.27)	1.01 (0.86–1.19)	1.07 (0.88–1.29)	1.28 (1.04–1.58)[d]	0.08
Cases, *n*	350	395	284	164	99	
Body fatness at adolescence, MV[a]	1 (Reference)	1.01 (0.88–1.17)	1.05 (0.90–1.23)	1.02 (0.85–1.23)	1.33 (1.06–1.67)	0.08
Body fatness at adolescence, MV+BMI[b]	1 (Reference)	1.00 (0.87–1.16)	1.03 (0.87–1.20)	0.99 (0.82–1.19)	1.27 (1.01–1.60)[d]	0.23
Men (HPFS)						
Cases, *n*	321	182	121	84	100	
Body fatness at childhood, MV[a]	1 (Reference)	1.01 (0.83–1.21)	0.99 (0.80–1.22)	1.01 (0.79–1.29)	1.12 (0.89–1.41)	0.48
Body fatness at childhood, MV+BMI[b]	1 (Reference)	1.00 (0.83–1.21)	0.95 (0.79–1.20)	0.96 (0.75–1.22)	1.04 (0.82–1.31)[d]	0.97
Cases, *n*	172	279	171	91	95	
Body fatness at adolescence, MV[a]	1 (Reference)	0.99 (0.82–1.20)	0.97 (0.78–1.20)	0.80 (0.62–1.04)	1.11 (0.86–1.44)	0.79
Body fatness at adolescence, MV+BMI[b]	1 (Reference)	0.96 (0.79–1.16)	0.91 (0.74–1.14)	0.73 (0.56–0.95)	0.98 (0.75–1.27)[d]	0.20

[a]Multivariable RRs were adjusted for age (in month), and height (continuous), smoking before age 30 (0, 1–4, 5–10, or >10 pack-years), history of colorectal cancer in a parent or sibling (yes or no), history of sigmoidoscopy/endoscopy (yes or no), current physical activity (<3, 3–< 27, 27+ MET-h/wk), regular aspirin use (yes or no), multivitamin use (yes or no), alcohol consumption (0–<5, 5–<10, 10–<15, or ≥15 g/d), current energy-adjusted total intake of calcium, vitamin D, folate, red meat, processed meat (all in tertiles), and postmenopausal hormone use (premenopausal, never, past, or current user; women only).
[b]Further adjustment for adult BMI (<25, 25–<27.5, 27.5–< 30, ≥30 kg/m^2).
[c]Using ordinal variables of somatotype, original 9 categories.
[d]*P* values for heterogeneity by sex were 0.19 for body fatness at childhood and 0.14 for body fatness at adolescence.

positively associated with risk of colorectal adenomas and cancer (44–46).

The association between adult BMI and colorectal cancer risk is generally more consistent and stronger among men (2–4), making the sex-specific associations in our study were somewhat unexpected. The stronger associations of colorectal cancer risk we observed among women may be due to chance, or may reflect differences among men and women in their recall of body fatness in childhood and adolescence with slightly better recall in women (26). Another possible explanation for sex difference derives from evidence that weight gain may be more of a risk factor in men than in women (47), possibly as a result of interactions between adult hormones and obesity in middle age. For example, testosterone in obese men may increase risk, whereas estrogen in obese women may decrease risk (48). Similar to the opposing effects of BMI on breast cancer risk depending on menopausal status, early life body fatness may have a different effect on risk compared with adult BMI. Clearly, additional studies on the association between body fatness and colorectal cancer risk that can evaluate risk across the lifespan will establish whether true gender differences exist and how these associations may vary by age.

Although mounting evidence suggests that colorectal cancer is heterogeneous by molecular features or anatomic location (49, 50), previous studies on early life body fatness and colorectal adenoma and cancer that evaluate subsites have been inconsistent. Modestly stronger positive associations for colon versus rectal cancer (16, 21) and distal adenomas versus proximal (38, 43) were noted in some but not all studies (17, 20). In fact,

Table 3. Multivariable RRs of colorectal cancer according to BMI (kg/m^2) at age 18 in the NHS and at age 21 in the HPFS (1988–2010)

	15–<19	19–<20.4	20.4–<21.9	21.9–<24.9	24.9–<27.5	27.5–<45 kg/m^2	P_{trend}[c]
Women (NHS)							
Cases, *n*	199	239	292	290	96	64	
MV[a]	1 (Reference)	1.01 (0.84–1.22)	1.09 (0.91–1.30)	1.12 (0.94–1.35)	1.31 (1.03–1.68)	1.53 (1.15–2.04)	<0.001
MV + BMI[b]	1 (Reference)	1.01 (0.83–1.22)	1.07 (0.89–1.29)	1.09 (0.90–1.32)	1.25 (0.97–1.62)	1.44 (1.06–1.95)[d]	0.002
Men (HPFS)							
Cases, *n*	83	100	133	282	134	76	
MV[a]	1 (Reference)	1.15 (0.85–1.55)	1.20 (0.90–1.59)	1.22 (0.93–1.58)	1.17 (0.86–1.56)	1.20 (0.86–1.68)	0.56
MV + BMI[b]	1 (Reference)	1.17 (0.87–1.58)	1.20 (0.91–1.60)	1.22 (0.94–1.58)	1.15 (0.86–1.55)	1.18 (0.84–1.65)[d]	0.71
	15–<18.5	**18.5–<23.0**	**23.0–<25.0**	**25.0–<27.5**	**27.5–<30**	**30–<45 kg/m^2**	**P_{trend}[c]**
Women (NHS)							
Cases, *n*	131	743	152	90	31	33	
MV[a]	1 (Reference)	1.06 (0.88–1.28)	1.21 (0.95–1.53)	1.33 (1.01–1.74)	1.43 (0.95–2.10)	1.71 (1.16–2.51)	<0.001
MV + BMI[b]	1 (Reference)	1.05 (0.88–1.26)	1.16 (0.91–1.48)	1.26 (0.95–1.67)	1.33 (0.89–2.00)	1.60 (1.07–2.39)[e]	0.009
Men (HPFS)							
Cases, *n*	61	346	190	133	47	29	
MV[a]	1 (Reference)	1.10 (0.84–1.46)	1.14 (0.84–1.53)	1.09 (0.79–1.51)	1.13 (0.76–1.69)	1.11 (0.70–1.76)	0.44
MV + BMI[b]	1 (Reference)	1.11 (0.84–1.47)	1.13 (0.84–1.52)	1.08 (0.78–1.49)	1.12 (0.75–1.67)	1.08 (0.69–1.72)[e]	0.57

[a]Multivariable RRs were adjusted for age (in month), and height (continuous), smoking before age 30 (0, 1–4, 5–10, or >10 pack-years), history of colorectal cancer in a parent or sibling (yes or no), history of sigmoidoscopy/endoscopy (yes or no), current physical activity (<3, 3–< 27, 27+ MET-h/wk), regular aspirin use (yes, no), multivitamin use (yes or no), alcohol consumption (0–<5, 5–<10, 10–<15, or ≥15 g/d), current energy-adjusted total intake of calcium, vitamin D, folate, red meat, processed meat (all in tertiles), and postmenopausal hormone use (premenopausal, never, past, or current user; women only).
[b]Further adjustment for adult BMI (<25, 25–<27.5, 27.5–<30, ≥30 kg/m^2).
[c]Continuous values of young adult BMI were used to calculate the P_{trend}.
[d]$P_{heterogeneity}$ by sex was 0.39.
[e]$P_{heterogeneity}$ by sex was 0.21.

Table 4. Stratum-specific multivariable[a] RRs of colorectal cancer in the NHS and HPFS

	Women						Men					
	Childhood			BMI at age 18			Childhood			BMI at age 21[d]		
	Somatotype 1	Somatotype ≥ 5	*P*	15–<19	27.5–<45	*P*	Somatotype 1	Somatotype ≥ 4	*P*	15–<19	27.5–<45	*P*
Birth weight (pounds)[b]												
<7	1 (Reference)	1.12 (0.64–1.96)	0.24	1 (Reference)	2.10 (1.26–3.50)	0.96	1 (Reference)	0.84 (0.56–1.23)	0.35	1 (Reference)	1.68 (1.08–2.60)	0.71
≥7	1.06 (0.83–1.35)	1.83 (1.33–2.51)		1.51(0.73–3.12)	2.39 (1.50–3.81)		1.24 (0.82–1.89)	1.49 (0.98–2.25)		1.65(0.99–2.76)	1.63 (0.94–2.82)	
Height, m												
<Median[c]	1 (Reference)	0.99 (0.71–1.38)	0.03	1 (Reference)	1.20(0.88–1.62)	0.18	1 (Reference)	1.03 (0.81–1.32)	0.99	1 (Reference)	1.19 (0.72–1.96)	0.59
≥Median	1.14 (0.96–1.36)	1.78 (1.36–2.33)		1.14 (0.80–1.62)	1.65 (1.17–2.33)		1.10 (0.88–1.38)	1.07 (0.81–1.41)		1.27 (0.75–2.12)	1.19 (0.58–2.44)	
Family history of colorectal cancer												
No	1 (Reference)	1.28 (1.01–1.62)	0.88	1 (Reference)	1.24 (0.98–1.56)	0.48	1 (Reference)	0.97 (0.78–1.19)	0.93	1 (Reference)	1.15 (0.84–1.59)	0.41
Yes	1.36 (1.10–1.68)	1.73 (1.14–2.63)		1.23 (0.92–1.63)	2.14 (1.36–3.35)		1.38 (1.02–1.86)	1.64 (1.15–2.34)		1.14 (0.79–1.65)	1.69 (0.93–3.06)	
Adult physical activity (MET-h/wk)												
<9	1 (Reference)	1.26 (0.91–1.75)	0.93	1 (Reference)	1.27 (0.96–1.68)	0.53	1 (Reference)	0.88 (0.60–1.29)	0.22	1 (Reference)	1.31 (0.76–2.28)	0.10
≥9	0.94 (0.79–1.12)	1.21 (0.92–1.61)		1.25 (0.90–1.73)	1.20 (0.83–1.74)		1.09 (0.84–1.42)	1.13 (0.85–1.50)		1.43 (0.77–2.62)	1.21 (0.71–2.06)	
Adult BMI (kg/m^2)												
<25	1 (Reference)	1.18 (0.85–1.66)	0.39	1 (Reference)	1.08 (0.73–1.601)	0.13	1 (Reference)	0.89 (0.64–1.23)	0.39	1 (Reference)	1.10 (0.68–1.77)	0.68
≥25	1.01 (0.84–1.21)	1.41 (1.09–1.83)		0.91 (0.43–1.94)	1.58 (1.22–2.03)		1.25 (1.00–1.56)	1.37 (1.08–1.69)		1.23 (0.72–2.10)	1.69 (1.06–2.72)	

[a]We adjusted for the same covariates as those listed in Table 2 footnote 2 except for the factors examined here.
[b]Birth weight was assessed in 1992 in the NHS (n = 695 cases) and in 1994 in the HPFS (n = 312 cases).
[c]Cutoffs were 1.65 m for women and 1.78 m for men.
[d]15–<20.4, 24.9–<45 kg/m^2 were used for the joint analysis on birth weight and BMI at 21 years in men due to small number of cases.

one study observed a significant inverse association for rectal adenomas (RR, 0.68; 95% CI, 0.49–0.95; ref. 43). Although we observed slightly stronger positive associations for distal colon cancer and rectal cancer for body fatness in young adulthood in women, overall our results were consistent across the colorectum.

Some limitations of this study warrant consideration. First, participants' memory to recall their early life body fatness may lead to measurement error. However, we do not expect such potential error have a substantial impact on our observations because previous work has indicated good validity of recalled childhood and adolescence body fatness by elderly adults (40). Because the recall of early life body fatness occurred years before cancer diagnosis, misclassification is likely to be random and lead to underestimation of the true associations. Nonetheless, studies that are able to directly measure early life body adiposity (e.g., waist circumference) may provide additional insights and confirmation of our findings. Second, our study population is primarily Caucasian and our results may not be generalizable to other ethnic and racial groups. However, the mechanistic pathways underlying the body fatness and cancer risk is unlikely to differ by race and ethnicity. Finally, our study is large overall, but we had limited statistical power to detect gender differences and evaluate whether the associations vary by cancer subsites or other factors.

Our study has some important strengths including its prospective design with long follow-up time and a high follow-up rate. In addition, we were able to adjust for possible confounders and evaluate whether the associations with early life body fatness were independent of adult body fatness.

In summary, findings from our study support the hypothesis that increased body fatness in childhood, adolescence, and young adulthood might be a risk factor for colorectal cancer, independent of adult obesity and predominantly in women. Future studies should investigate the potential mechanisms behind this association, as well as determine whether a true gender difference exists. More broadly, these results provide additional justification for the importance of reducing childhood obesity.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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Early Life Body Fatness and Risk of Colorectal Cancer in U.S. Women and Men––Results from Two Large Cohort Studies

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