Research Article

Cancer Epidemiology, Biomarkers & Prevention

Childhood Body Mass Index Is Associated with Risk of Adult Colon Cancer in Men: An Association Modulated by Pubertal Change in Body Mass Index

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Abstract

Background: The relative contribution of childhood and pubertal body mass index (BMI) for the risk of adult colorectal cancer is not known. The aim of this study was to evaluate the independent associations for childhood BMI and pubertal BMI change with risk of colorectal cancer in men.

Methods: We included 37,663 men born in 1946 to 1961 who had weight and height measured at 8 (childhood) and 20 (young adult age) years of age available from the BMI Epidemiology Study. Information on colorectal cancer was retrieved from the Swedish National Patient Register (257 cases of colon cancer and 159 cases of rectal cancer).

Results: Childhood BMI at 8 years of age [HR, 1.19 per SD increase; 95% confidence interval (CI), 1.06–1.33], but not pubertal BMI change (HR, 1.02; 95% CI, 0.90–1.15), was associated with increased risk of colon cancer. Due to a significant interaction between childhood BMI and pubertal BMI change ($P < 0.001$), we stratified the analyses according to the median of pubertal BMI change. Childhood BMI was associated with risk of colon cancer in individuals with a pubertal BMI change above, but not below, the median (above: HR = 1.48, 95% CI, 1.26–1.74; below: HR = 0.95, 95% CI, 0.80–1.12). Neither childhood BMI nor pubertal BMI change was associated with rectal cancer.

Conclusions: High childhood BMI was associated with increased risk of colon cancer only if it was followed by a pubertal BMI increase above the median.

Impact: Further studies should evaluate prepubertal childhood BMI in relation to pubertal BMI change and BMI in middle age for the risk of colon cancer.

Introduction

As the third most common cancer in adults worldwide, colorectal cancer represents a heavy burden to public health (1). Developed Western countries rank highest in the world in colorectal cancer prevalence and a rapid increase in the incidence often follows a country's transition from low income to high income (2, 3).

Modifiable risk factors for colorectal cancer include physical inactivity, a high calorie/low fiber diet, high body mass index (BMI), excessive alcohol consumption, and smoking (3). A high BMI at different time points from young adult age to old age has been reported to increase the risk of colorectal cancer (4–8). Evidence of an association between high BMI in childhood and increased risk of colon but not rectal cancer was recently presented in a well-powered Danish study (9), but other reports have been unable to detect such an association (10, 11). Moreover, the Danish study also demonstrated a significant association between height during childhood and colon cancer (9). The role for pubertal BMI change has not been evaluated, and consequently, the association between childhood BMI and colorectal cancer independent of pubertal BMI change is not known (12).

We recently made the novel observation that childhood BMI at 8 years of age and pubertal BMI change (BMI at 20 years of age – BMI at 8 years of age) correlate only marginally, indicating that these two distinct developmental BMI parameters have the potential to contribute nonoverlapping information as risk markers for adult diseases (13). This notion is supported by our recent findings that excessive pubertal BMI increase is an independent risk factor for cardiovascular mortality, heart failure, and stroke (13–15). The BMI Epidemiology Study was initiated with the overall objective to study the association between BMI during development and adult disease and includes BMI variables reflecting childhood, puberty, and young adulthood. We hypothesize that BMI during the physiologically distinct developmental periods of childhood and puberty are of importance for the risk of adult colon cancer. The aim of this study was to evaluate the independent association for childhood BMI and pubertal BMI change with risk of colorectal cancer in men.

Materials and Methods

Study population

Birth weight as well as measurements of height and weight were collected from School Health Care records and military conscription tests for men born between 1945 and 1961 in Gothenburg, Sweden. Using the included participants personal identity

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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numbers (PIN), the cohort was linked to national disease registers. The cohort has been described previously (13–15). Participants with data available for calculation of both childhood and young adult BMI were included in this study (n = 37,663). The included participants were followed from the age of 20 until censoring due to colon or rectal cancer diagnosis, death, migration, or until December 31, 2013 whichever came first (Supplementary Fig. S1).

The study was approved by the ethics committee of the University of Gothenburg, Gothenburg, Sweden, and the requirement for written informed consent was waived. There was no commercial sponsorship.

Exposures

Prepubertal childhood BMI was calculated using all paired height and weight measurements in the period between 6.5 and 9.5 years of age, and for young adult BMI in the period between 17.5 and 22 years of age, and age-adjusted to 8 years and 20 years, respectively, as described previously (13, 14). Pubertal BMI change was defined as the difference between young adult BMI and childhood BMI, and young adult BMI thereby is the sum of childhood BMI and pubertal BMI change. Childhood overweight (BMI $\geq$ 17.9 kg/m.) was defined according to the Centers for Disease Control and Prevention's (CDC, Atlanta, GA) cutoff at 8 years of age (16). Overweight at young adult age was defined as a BMI of 25.0 kg/m^2 or more. Childhood height was calculated with a model similar to childhood BMI. All height measurements between 6.5 and 9.5 years of age were used and age-adjusted with a linear regression model to age 8 years. Adult height was the last recorded height after 17.5 years of age.

Outcomes

Linkage to registers held by the National Board of Health and Welfare and Statistics Sweden was done with the individuals' 10-digit PIN. Cancer diagnoses were coded according to the International Classification of Diseases (ICD) system. The risks of colon and rectal cancer development were analyzed separately. Colon cancer was defined as C18 in ICD10 and as 153 in ICD8 and 9. Rectal cancer was defined as C19–20 in ICD10, 154A–B in ICD9, and 154.01 and 154.11 in ICD8.

Statistical analyses

Differences between the group with overweight at 8 years of age and those with normal weight at the same age were tested using χ^2 test for dichotomous variables and student t test for continuous variables. Childhood BMI and young adult BMI were log-transformed and standardized, and childhood height, birth weight, and pubertal BMI change were standardized when used in the Cox regression models. The standardization was done within the study population, having zero mean and unit variance. The standard score (Z) was calculated as $Z = (x-\mu)/\sigma$. μ is the mean of the study population and σ is the SD of the study population. The standardization of BMI and height variables was used to express the effect sizes in SDs. The effect sizes for the associations of the different BMI parameters were easier to compare when using standardized values. Log-transformation of skewed variables produced variables more close to a normal distribution.

The study subjects' highest achieved education level (high, medium, or low) was retrieved from demographic registers at Statistics Sweden. The assumption of proportionality was confirmed for all variables. Possible interactions were assessed by addition of an interaction term in the linear Cox regression models, and a P value of less than 0.05 for the interaction term was interpreted as a statistically significant interaction. The interaction term included the two parameters (continuous) of interest multiplied by each other. Because of an interaction between childhood BMI and pubertal BMI change ($P < 0.001$ for the interaction term, childhood BMI $\times$ pubertal BMI change) in the entire cohort, the multivariate analyses were stratified according to the median of pubertal BMI change. The Cox regression models were adjusted for country of birth and birth year. Nonlinear associations were evaluated by inclusion of a quadratic term of the variable of interest in the Cox regression.

Sensitivity analyses were performed by censoring the first 10, 20, and 30 years of follow-up, respectively, and by restricting the analysis to subjects born in Sweden and with both parents born in Sweden. Kaplan–Meier survival plots and the test for proportionality were done in R (version 3.2.3) with the survival and regression modeling strategies packages. For all other statistical analyses we used SPSS (version 24).

Results

We followed 37,663 Swedish men from 20 years of age for a mean of 37.7 (SD, 8.6) years. 257 cases of colon cancer were diagnosed during 1,420,794 person-years follow-up for colon cancer, and 159 cases of rectal cancer were diagnosed during 1,421,124 person-years follow-up for rectal cancer (Table 1).

Associations with colon cancer

Childhood BMI at 8 years of age was associated with the risk of colon cancer in a Cox proportional hazards regression (HR, 1.19 per SD increase; 95% CI, 1.06–1.33). Neither pubertal BMI change (BMI at age 20 – BMI at age 8), nor young adult BMI at 20 years of age were significantly associated with increased risk of colon cancer, although young adult BMI showed a tendency (HR, 1.11 per SD increase; 95% CI, 0.98–1.25; Table 2).

As we found a significant interaction between childhood BMI and pubertal BMI change for the risk of colon cancer ($P < 0.001$) in the entire cohort, the subsequent analyses were stratified by splitting the cohort on the median (5.4 kg/m^2) according to pubertal BMI change. Of note, childhood BMI showed a significant linear association with risk of colon cancer in individuals above, but not below, the median of pubertal BMI change (Figs. 1 and 2). The association between childhood BMI and colon cancer in the stratified analysis was not altered by adjustment for young adult BMI (Table 3).

A Kaplan–Meier survival plot showed a higher risk of colon cancer in individuals in the upper half of childhood BMI compared with the lower childhood BMI half ($P < 0.01$) in the stratum above, but not below, the median of pubertal BMI change (Supplementary Fig. S2). Assessment with cumulative incidence plots did not indicate that there was a non-colon cancer mortality disturbing the current finding of increased risk of colon cancer for participants with a high childhood BMI (upper half) compared with participants with low childhood BMI (lower half) in subjects with a pubertal BMI increase above the median (Supplementary Fig. S3A–S3D).

Table 1. Cohort descriptives

Exposures	Entire cohort (n = 37,663)	Childhood normal weight (n = 35,306)	Childhood overweight (n = 2,357)
Childhood BMI (SD), kg/m^2	15.7 (1.4)	15.5 (1.0)	19.2 (1.4)[a]
Young adult BMI (SD), kg/m^2	21.4 (2.5)	21.1 (2.2)	25.0 (3.4)[a]
Pubertal BMI change (SD), kg/m^2	5.6 (2.0)	5.6 (1.9)	5.7 (3.2)[a]
Birth weight[b] (SD), kg	3.58 (0.56)	3.57 (0.55)	3.72 (0.56)[a]
Childhood overweight, *n* (%)	2,357 (6.3%)	N/A	N/A
Young adult overweight, *n* (%)	2,789 (7.4%)	1,799 (5.1%)	990 (42.0%)[a]
Country of birth[c]			
Sweden n (%)	31,402 (83.4%)	29,444 (83.4%)	1,958 (83.1%) NS
Other	6,261 (16.6%)	5,862 (16.6%)	399 (16.9%) NS
Outcomes	No of cases		
Colon cancer diagnosis, *n* (%)	257 (0.7%)	231 (0.7%)	26 (1.1%)[d]
Rectal cancer diagnosis, *n* (%)	159 (0.4%)	148 (0.4%)	11 (0.5%) NS

NOTE: Descriptive statistics for the cohort (n = 37,663). Childhood refers to 8 years of age. Young adulthood refers to 20 years of age. Pubertal BMI change is the change in BMI between 8 and 20 years of age. Childhood overweight was defined as BMI >17.9 kg/m^2 (16), young adult overweight was defined as BMI >25 kg/m^2.
[a]P < 0.001, NS = not significant (χ^2 test for dichotomous variables and student t test for continuous variables, vs. childhood normal weight).
[b]n = 35,653.
[c]Sweden, if child and both parents were born in Sweden.
[d]P < 0.05.

Association between childhood and young adult overweight and risk of colon cancer

Children with overweight at 8 years of age demonstrated a substantially increased risk of adult colon cancer (Table 2). Young adult overweight was not significantly associated with colon cancer, but displayed a tendency of increased risk (HR, 1.46; 95% CI, 0.96–2.22; Table 2). In the analyses stratified by the median of pubertal BMI change, the association between childhood overweight and risk of colon cancer was pronounced above (HR, 2.81; 95% CI, 1.70–4.64), but not below (HR, 0.98; 95% CI, 0.48–1.99), the median of pubertal BMI change (Fig. 2).

Adjustment for childhood and adult height

Neither childhood height at age 8 nor adult height was associated with the risk of colon cancer (Table 2). No statistically significant interaction was seen between childhood height and childhood BMI for the association with colon cancer incidence. The inclusion of childhood height or adult height as covariates in the Cox regression model did not alter the association between childhood BMI and adult colon cancer risk (Table 3).

Table 2. HRs for colon cancer in relation to anthropometric variables in 37,663 Swedish men followed for a mean of 37.7 (8.6) years after 20 years of age

Exposure variable	HR (95% CI) per SD increase
Childhood BMI	1.19 (1.06–1.33)
Pubertal BMI change	1.02 (0.90–1.16)
Young adult BMI	1.11 (0.98–1.25)
Childhood height	1.05 (0.93–1.18)
Adult height	0.97 (0.86–1.10)
	HR (95% CI)
Childhood overweight	1.78 (1.19–2.67)
Young adult overweight	1.46 (0.96–2.22)

NOTE: HRs for colon cancer according to anthropometric variables were calculated using Cox proportional hazards regression. Childhood refers to 8 years of age. Young adult BMI refers to 20 years of age. Pubertal BMI change is the change in BMI between 8 and 20 years of age. Adult height refers to the last recorded height after 17.5 years of age. The model is adjusted for birth year and country of birth. Number of colon cancer diagnoses n = 257, total cohort N = 37,663. The CDC cutoff for childhood overweight was used (BMI > 17.9 kg/m^2), young adult overweight was defined as BMI > 25 kg/m^2.

Adjustment for birth weight and educational level

Birth weight was available in a subsample of the current cohort (n = 35,653). Adjustment for birth weight did not alter any of the described associations of childhood BMI and colon cancer within strata or in the entire cohort (Table 3). Adjustment for the highest achieved educational level was available for a subset of the cohort (n = 35,963), and again, the described associations between childhood BMI and colon cancer was not altered within strata (before adjustment HR = 0.96, 95% CI, 0.81–1.13 below and HR = 1.49, 95% CI, 1.28–1.74 above the median of pubertal BMI change; after adjustment HR = 1.00, 95% CI, 0.85–1.19 below, and HR = 1.47, 95% CI, 1.25–1.72 above the median of pubertal BMI change).

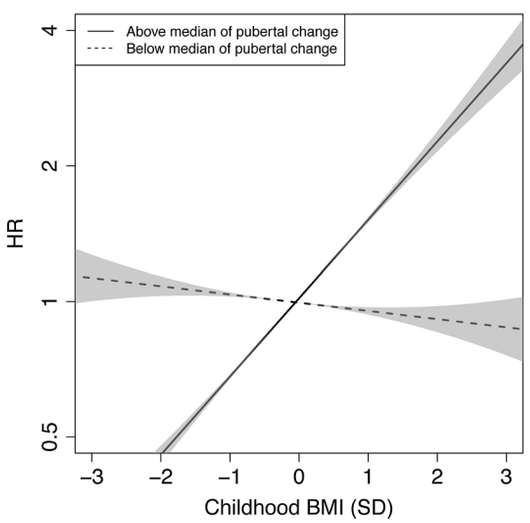

Figure 1.
Adjusted HRs for colon cancer in relation to childhood BMI stratified by the median of pubertal BMI change. HRs were calculated using Cox proportional hazards regression. Separate analyses above the median of pubertal BMI change (n = 18,832), and below the median of pubertal BMI change (n = 18,831). Analyses were adjusted for birth year and country of birth. Shaded areas indicate 95% CIs.

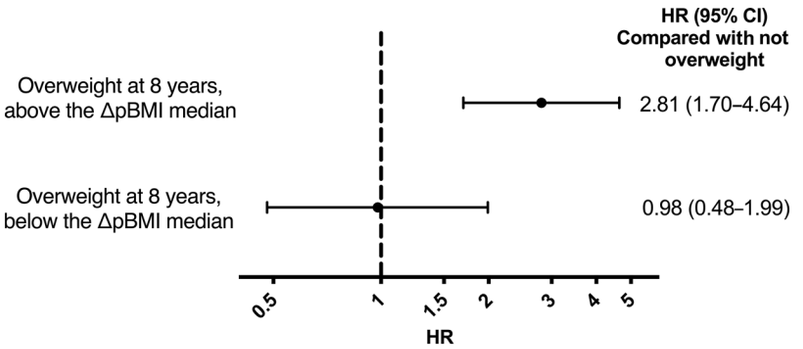

Figure 2.
Adjusted HRs for colon cancer in relation to childhood overweight stratified by the median of pubertal BMI change. HRs were calculated using Cox proportional hazards regression. Separate analyses above the median of pubertal BMI change ($n = 18,832$), and below the median of pubertal BMI change ($n = 18,831$). Analyses were adjusted for birth year and country of birth. In each analysis the non-overweight individuals are the reference. ΔpBMI, pubertal BMI change.

Sensitivity analyses

In sensitivity analyses, exclusion of the first 10 years of follow-up (participants only followed after age 30 years, 1,273 censored) did not alter the described association between childhood BMI at 8 years of age and risk of colon cancer in individuals with a pubertal BMI change above the median. Similar results were seen when omitting the first 20 and 30 years of follow-up (Supplementary Table S1). When we split the follow-up at the median age of the cases, the associations between childhood BMI and the risk of early (before 56.8 years of age) and late (after 56.8 years of age) adult colon cancer was similar as with the complete follow-up period (Supplementary Table S2).

We also assessed a subpopulation only including boys born in Sweden with parents born in Sweden. The described associations for childhood BMI with adult colon cancer incidence were similar in this subpopulation of Swedish-born boys (HR = 1.57 per SD increase above the median of pubertal BMI change, 95% CI 1.33–1.86, and HR = 0.95 per SD increase below the median of pubertal BMI change, 95% CI 0.79–1.15).

Associations with colon cancer subsites and rectal cancer

Less-powered exploratory subanalyses of the associations between childhood BMI and the risk of adult proximal and distal colon cancer separately indicated similar results as when all cases of adult colon cancer were analyzed together (Supplementary Table S3).

Neither childhood BMI nor pubertal BMI change were associated with adult rectal cancer risk (Table 4).

Table 3. Cox regression analyses of childhood BMI stratified by the median of pubertal BMI change in relation to adult colon cancer risk with adjustments for related variables

	HR (95% CI) per SD increase of childhood BMI–stratified analyses	
Childhood BMI adjusted for	**Below median of ΔpBMI *N* = 18,831**	**Above median of ΔpBMI *N* = 18,832**
Base model	0.96 (0.81–1.13)	1.49 (1.28–1.74)
Young adult BMI	1.04 (0.79–1.35)	1.45 (1.12–1.86)
Childhood height	0.95 (0.80–1.13)	1.51 (1.28–1.77)
Adult height	0.99 (0.84–1.18)	1.50 (1.28–1.75)
Birth weight[a]	0.93 (0.77–1.11)	1.49 (1.27–1.75)

Abbreviation: ΔpBMI = Pubertal BMI change.
NOTE: HRs were calculated using Cox proportional hazards regression. Childhood refers to 8 years of age. Young adult BMI refers to 20 years of age. Pubertal BMI change is the change in BMI between 8 and 20 years of age. Adult height refers to the last recorded height after 17.5 years of age. Model adjustment: base model was adjusted for birth year and country of birth. All other models were adjusted for birth year, country of birth, and the given variable.
[a]The analysis adjusted for birth weight $n = 35,653$, number of cases = 245.

Discussion

In this population-based study, we investigated the associations between BMI during the physiologically distinct developmental periods, childhood and puberty, and the risk of adult colon and rectal cancer in men. We found that BMI at 8 years of age, representing childhood, showed a significant association with adult risk of colon cancer, while pubertal BMI change per se did not. Still, pubertal BMI change did modulate the association between childhood BMI and colon cancer as illustrated by the fact that a high childhood BMI was associated with increased risk of colon cancer only if followed by a pubertal BMI increase above the median. Thus, childhood BMI was associated with adult colon cancer risk and this association was modulated by pubertal BMI change.

A high adult BMI, and to a lesser extent a high BMI in young adulthood, are established risk factors for colorectal cancer (5, 6, 17, 18), but studies addressing the associations between childhood BMI and risk of adult colorectal cancer are scarce. A Danish study demonstrated an association between childhood BMI between 7 and 13 years of age and increased risk for colon, but not rectal cancer (9). Other studies reported absence of a significant association between childhood BMI and colon cancer, but these studies were not adequately powered to detect such an association (10, 11, 19), or may have been hampered by the use of self-reported childhood body size (20, 21). Very recently, a follow-up of the Danish study reported that overweight at age 7 or 13 was associated with increased risk of adult colon cancer if the overweight status was maintained until young adulthood, but not if the overweight status was normalized in adulthood (8).

Table 4. HRs for rectal cancer in relation to anthropometric variables in 37,663 Swedish men followed for a mean of 37.7 (8.6) years after 20 years of age.

Exposure variable	**HR (95% CI) per SD increase**
Childhood BMI	0.99 (0.85–1.16)
Pubertal BMI change	0.88 (0.74–1.04)
Young adult BMI	0.88 (0.75–1.04)
Childhood height	1.02 (0.87–1.19)
Adult height	1.04 (0.88–1.21)
	HR (95% CI)
Childhood overweight	1.17 (0.63–2.16)
Young adult overweight	1.04 (0.56–1.92)

NOTE: HRs for rectal cancer ($n = 159$) according to anthropometric variables were calculated using Cox proportional hazards regression. Childhood refers to 8 years of age. Young adult BMI refers to 20 years of age. Pubertal BMI change is the change in BMI between 8 and 20 years of age. Adult height refers to the last recorded height after 17.5 years of age.
The model is adjusted for birth year and country of birth. Total cohort $N = 37,663$.

These results are in concordance with the results from this study, although it should be emphasized that BMI at age 13 is affected both by adiposity and by pubertal timing and is therefore ambiguous. In contrast, BMI change during puberty, used in this study, correlates only marginally with childhood BMI (13) and reflects the overall BMI change during the complete pubertal period.

To analyze the relative contribution of childhood and puberty for the risk of adult colon and rectal cancer, we used the developmental parameters—childhood BMI at 8 years and pubertal BMI change. We demonstrate a significant interaction between childhood BMI and pubertal BMI change for the risk of adult colon cancer and subsequent analyses were therefore stratified according to the median of pubertal BMI change. Childhood BMI was strongly associated with adult colon cancer risk in individuals with a pubertal BMI change above, but not below the median. The most pronounced effect, a nearly 3-fold increase in the risk for colon cancer, was seen for individuals with childhood overweight and a subsequent BMI increase during puberty above median. These findings indicate that childhood BMI is a determinant, and pubertal BMI change is a modulator, of the risk of adult colon cancer.

Childhood and puberty are two physiologically distinct developmental periods. Growth hormone and insulin growth factor-1 are the major anabolic hormones mediating childhood growth, while the pubertal period is characterized by secretion of sex steroids and pubertal growth. Colon cancer development has been linked to high levels of insulin-like growth factor (IGF) and/or overexpression of IGF receptors (22). Other proposed links between obesity and colon cancer include systemic and local inflammation (7), the metabolic syndrome, insulin resistance, and dysbiosis (23).

In this study we demonstrate that childhood BMI was associated with colon cancer and this association was modulated by pubertal BMI change. These findings indicate that both high childhood BMI and a large BMI increase during puberty are of importance for the risk of colon cancer later in life, but the study was not designed to detect a causal relationship. Childhood may represent a critical window for the metabolic programming that affects risk factors for colorectal cancer, and it is plausible that growth factors play an important role as mediators for the association between childhood BMI and colon cancer (24). The adverse developmental trajectory regarding risk of colon cancer also includes that the high childhood BMI is followed by a pubertal BMI increase above the median, possibly affecting the amount of visceral fat. We speculate that high childhood BMI, via metabolic programming, catalyzes early pathophysiologic steps of colon cancer, and that these are modulated to progress if the high childhood BMI is followed by a large BMI increase during puberty. We therefore propose that BMI during development confers increased risk for adult colon cancer in a two-stage process; a high childhood BMI followed by a pubertal BMI increase above the median.

We have previously observed that childhood BMI and pubertal BMI change correlate only marginally, indicating that they contribute nonoverlapping information as risk markers for adult diseases (13). Our previous findings demonstrate that pubertal BMI change, but not childhood BMI, is associated with adult risk of cardiovascular disease (13–15). In contrast, we herein present evidence that childhood BMI associates with the risk of adult colon cancer. Taken together, these findings suggest that excess BMI during separate developmental periods (childhood or puberty) may contribute differently to the risk of adult diseases.

The observational nature of our study precludes making conclusive statements about the observed associations, but our findings can be useful for hypothesis generation. On the basis of our findings in this study, the risk of adult colon cancer might be reduced for the overweight 8-year-old boy if excessive BMI increase during puberty is avoided. Our findings suggest that monitoring BMI during childhood and puberty could prove to be a useful public health strategy.

In the study by Jensen and colleagues, an association between childhood height and the risk of adult colon cancer was presented, but whether or not childhood height and childhood BMI were associated with risk of adult colon cancer independently of each other was not reported (9). In our study, childhood height did not significantly associate with the risk of colon cancer, and when childhood height was included as a covariate in the analysis, the association between childhood BMI and risk of adult colon cancer was unaltered.

The absence of associations between childhood BMI, pubertal BMI change, or young adult BMI and adult rectal cancer risk align well with existing literature illustrating that colon and rectal cancer are diverse entities regarding risk factors (9, 25, 26).

An important limitation of this study is that we could not control for several important risk factors (e.g., smoking, dietary habits, and exercise) or for BMI at middle age. The current cohort includes primarily Caucasian men and, therefore, the results may have limited generalizability to other ethnicities. This study had limited power for subsite analyses of colon cancer. As Sweden did not have mandatory female military conscription, we were unable to retrieve young adult BMI for women, limiting our study to men only. BMI reflects lean, fat, and to a lesser extent, bone mass, and given the retrospective design of this study we are unable to evaluate the associations with these BMI components separately. The strengths of this study include the large size of the cohort, the extended adult follow-up, the possibility to adjust for educational level at middle age, and a range of important anthropometric variables. The population-based nature of the cohort and the near complete participation in the free school health care with repeated standardized measurements of height and weight, strongly reduces risk of selection bias. In addition, the Swedish national disease registers are of recognized high quality which permits a near-complete follow-up of subjects in the study and their diagnoses as reported by the health care provider (27).

In conclusion, a high childhood BMI is associated with increased risk of colon cancer. Pubertal BMI change modulates this association, illustrated by the fact that high childhood BMI was associated with increased risk of colon cancer only if followed by a pubertal BMI increase above the median.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: J. Célind, C. Ohlsson, M. Bygdell, J.M. Kindblom
Development of methodology: J. Célind, C. Ohlsson, M. Bygdell, J.M. Kindblom
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Célind, M. Bygdell, J.M. Kindblom
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J. Célind, C. Ohlsson, M. Nethander, J.M. Kindblom
Writing, review, and/or revision of the manuscript: J. Célind, C. Ohlsson, M. Bygdell, M. Nethander, J.M. Kindblom

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J. Célind, J.M. Kindblom
Study supervision: J.M. Kindblom

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