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Height as an independent anthropomorphic risk factor of colorectal cancer

Ben Boursi, M.D.^{1,2,3,*}, Kevin Haynes, PharmD, M.S.C.E¹, Ronac Mamtani, M.D. M.S.C.E¹,
and Yu-Xiao Yang, M.D., M.S.C.E¹

¹Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA

²The Integrated Cancer Prevention Center, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel

³Tel-Aviv University, Tel-Aviv, Israel.

Abstract

Background—Previous studies showed an association between height and CRC. None of those works adjusted the association to known risk factors, such as diabetes mellitus and chronic exposure to aspirin/NSAIDs. Only two works evaluated the risk among males.

Methods—We conducted a nested case-control study using a large population-based medical records database from the UK. Study cases had any CRC code after the age of 40. Subjects with known familial CRC syndromes or IBD were excluded from the study. For every case, up to 4 eligible controls matched on age, sex, practice-site, and duration of follow-up before index date were selected using incidence-density sampling. Height was defined as the last measurement before index date. The odds ratios (OR) and 95% confidence-intervals (CIs) for CRC were calculated for height quartiles as well as for every 10cm increase in height using conditional logistic regression analysis, and adjusted for BMI, alcoholism, smoking history, diabetes mellitus, chronic NSAIDs use and previous screening colonoscopies.

Results—9,978 cases and 26,847 controls were identified. The adjusted OR for CRC in subjects at the highest compared to the lowest height quartiles was 1.25 for males (95%CI 1.14-1.37) and 1.25 for females (95%CI 1.12-1.39). The adjusted OR associated with per 10cm increase in height was 1.10 (95%CI 1.05-1.15) for males and 1.16 (95%CI 1.10-1.23) for females. The risk remained persistent when analyzing different age groups.

Conclusions—Height is an independent risk factor in both males and females for CRC.

Keywords

height; colorectal; cancer; risk factor; screening

Please address correspondence to: Yu-Xiao Yang, M.D., M.S.C.E. Division of Gastroenterology, Department of Medicine Department of Epidemiology and Biostatistics Center for Clinical Epidemiology and Biostatistics Perelman School of Medicine at the University of Pennsylvania 733 Blockley Hall, 423 Guardian Drive Philadelphia, Pennsylvania 19104-6021, U.S.A. Fax: (215)349-5915; Telephone: (215)573-5027 yangy@mail.med.upenn.edu.

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Introduction

Body mass index (BMI) is a well-known anthropomorphic variable that was shown in previous studies to be associated with increased colorectal cancer (CRC) incidence and outcome, more prominently in males than in females (1-4). Similar to BMI and weight, height serves as a proxy for several genetic and environmental exposures in early life, such as socio-economic status, energy intake and growth factor levels, which may impact cancer risk later in life (5-8). Insulin-like growth factor-1 concentration is associated with both growth during childhood and a higher risk for prostate, breast and colorectal cancers (9-12). Likewise, energy restriction during childhood is associated with lower CRC risk in adults (13, 14). Additional mechanisms underlying the association between height and cancer risk relates to the larger number of cells in taller persons, as expressed in increased colonic length and skin surface area (15).

Previous studies evaluated the association of height with cancers in different anatomic sites and demonstrated increased risks for melanoma, breast, ovary, prostate, lung and colorectal cancers as well as elevated site specific mortality (16-22). For CRC the effects of sex, tumor site and smoking status were evaluated as possible modifiers of the association with conflicting results (16,22). Two previous studies, the Netherlands cohort study (NLCS) (23) and a large retrospective study from Norway (24) evaluated the association of increasing height on CRC risk in males, with conflicting results. In the first, increasing height (per 5cm) was not associated with increased CRC risk (hazard ratio [HR] 0.96, 95% confidence interval [CI] 0.8-1.04), while in the second study an increase in height both in males and females was associated with increased CRC risk (relative risk [RR] 1.14, 95% CI: 1.11-1.16 and 1.17, 95%CI 1.14-1.20, respectively). Two prospective cohorts in women, the million women study in the UK and the Canadian national breast screening study, showed a lower HR for the association between height and CRC in women who were current smokers compared to never smokers (22, 25).

Several other studies demonstrated higher risk of tumors located in the proximal colon among taller individuals (24, 26), while other works showed a higher risk for distal lesions (23).

Importantly, none of the prior studies adjusted for important confounders to this association such as diabetes mellitus, ischemic heart disease and chronic exposure to aspirin or NSAIDs (22,25,27) and only one study adjusted for previous colorectal cancer screening (22).

The goal of the current study was to evaluate association between height and CRC in a large population-based cohort while controlling for known risk factors for CRC.

Methods

Study Design

We conducted a nested case-control study using The Health Improvement Network (THIN), a large population-based electronic medical records database from the United Kingdom

(UK). The study was approved by the Institutional Review Board at the University of Pennsylvania and by the Scientific Review Committee of THIN.

Data source

The THIN database contains comprehensive medical records on approximately 10 million patients treated by general practitioners throughout the UK and representative of the general UK population. All practices contributing data to THIN follow a standardized protocol of entering information and transmitting information to the central database. Each medical diagnosis is defined using Read diagnostic codes; each medication is uniquely coded using multiplex codes. Data quality is monitored through routine analysis of the entered data (28,29). Hundreds of epidemiologic studies have been performed using the THIN database, showing excellent quality of information on prescriptions and medical diagnoses (30).

Study cohort

All people receiving medical care from 1995 to 2013 from a THIN practitioner were potentially eligible for inclusion (Figure 1). Subjects with a history of familial CRC syndromes, inflammatory bowel disease (IBD) or prevalent CRC were excluded, as well as subjects without documented height before index date. Follow-up started at the later of either the date when the THIN practice started using the electronic medical record software or 183 days after the date at which the patient registered with their general practitioner and ended on the index date (defined below). Subjects who were diagnosed with CRC within 183 days after initiation of the follow-up period were excluded in order to avoid prevalent cases (31).

Case selection

Cases were defined as all individuals in the cohort that were given at least one medical Read code for CRC during the follow-up period and were more than 40 years old at the time of diagnosis. Index date was defined as the date of first CRC diagnosis. Of note, a previous study demonstrated that the incidence of CRC in THIN was comparable to the incidence in the entire population of the UK as reported in cancer registry data (32).

Selection of controls

Selection of the control group was based on incidence density sampling (33). The potentially eligible control pool to each case was comprised of all individuals from the THIN database who remained at risk to CRC (i.e., not yet developed CRC or underwent colectomy) on the calendar date when the case was first diagnosed with CRC. Up to four eligible controls were matched with each case in regards to age (using age group categories of 5 years), sex, practice site, and both duration and calendar period of follow-up. Controls were assigned the same index date as their matched case.

Exposures and Covariates

The exposure of interest was height, measured in meters and defined based on the last recorded measurement before index date. We also examined a comprehensive list of potential confounders that are either known or suspected risk factors for CRC such as

lifestyle parameters including BMI (<25, 25-29, 30-39, >40), smoking history (current, past or never), alcohol consumption (any use and alcoholism/alcohol dependence), previous (i.e., > 2 years before index date) colonoscopy; medical co-morbidities (including diabetes mellitus ischemic heart disease and connective tissue disease¹, all with initial diagnosis before index date); and chronic use of Aspirin/NSAIDs (first prescription at least 12 months before index date last prescription within 6 months before index date and cumulative duration of therapy more than 365 days).

Statistical Analysis

The baseline characteristics of cases and controls were compared using chi square tests for categorical variables and t-tests for continuous variables. The primary analysis consisted of multivariable conditional logistic regression to estimate the odds ratios (OR) and 95% CI for the association between CRC and height. In this analysis, height was

Results

The study included 9,978 CRC patients and 26,847 matched controls (Figure 1). The characteristics of cases and controls were shown in Table 1. As expected, cases were more likely to have a medical history of diabetes mellitus (17.3% vs. 15%), BMI above 40 (3.2% vs 2.6%), history of ever smoking or alcoholism and less likely to be chronic users of aspirin/NSAIDs. Of note, the prevalence of presumed screening colonoscopy in the study population was low (2.0% of cases and 2.7% of controls). (Table 1).

For both men and women, univariate analysis demonstrated a significant increase in CRC risk associated with height both as a continuous variable and by quartiles (Table 2). The effect estimates were generally unchanged in the multivariable analysis (Table 2). The adjusted OR for CRC when comparing the highest height quartile to the lowest height quartile was 1.25 (95% CI: 1.14-1.37) for males and 1.25 (95% CI 1.12-1.39) for females. The adjusted ORs for CRC associated for every 10cm increase in height was modestly higher for females (OR 1.16, 95% CI: 1.10-1.23) compared to males (OR 1.10, 95% CI: 1.05-1.15) (Table 2).

We further evaluated whether the association between CRC risk and height varied by age (i.e., above and below 60 years). Among men, the association between height and CRC risk was slightly more pronounced among men over 60 years (OR 1.11 vs 1.05). However, there was no statistically significant interaction by age groups (Table 3). Among women, the association between height and CRC were similar across the two age groups (Table 4).

¹Rheumatoid arthritis and systemic lupus erythematosus. entered into the model as a categorical variable using quartiles of increasing height (<1.7, 1.7-1.75, 1.75-1.79, >1.79 in males and <1.56, 1.56-1.6, 1.6-1.65, >1.65 in females) and as a continuous variable (per 10cm increase). The analysis was adjusted to all the confounders that were measured: BMI, alcohol consumption, smoking history, chronic NSAIDs use, diabetes mellitus, ischemic heart disease, connective tissue disease and previous events of screening colonoscopy. Additionally, the results were stratified according to sex, age (below and above 60 years) and smoking (current past or never) in order to assess for possible effect modifiers previously described in the literature. All calculations were done using STATA 13 (College Station, TX).

Discussion

The current population based nested case-control study demonstrated that increasing height is associated with an elevated CRC risk. The effect of height on CRC risk was similar in both men and women, in different age groups (i.e., above and below 60 years), and when analyzed as a continuous or categorical variable. Unique aspects of the present work include matching cases and controls on practice site and socio-economic status and adjustment for potential confounders such as diabetes mellitus, BMI, smoking, alcoholism, chronic aspirin/NSAIDs use and previous screening colonoscopies. The association –between height and CRC was independent of those known cancer risk factors and adjustment did not change the crude OR.

The association between height and cancer risk has been examined in a limited number of studies. Prior studies have evaluated overall cancer risk and were thus unable to adjust for CRC specific risk factors. One cohort study from the Netherlands (NLCS) focused on CRC, however it adjusted only for smoking, alcohol use, education level and physical activity and relied on self-reported height and weight data, which may be prone to misclassification or recall bias. A major strength of THIN, the data source used in this study, is that height data are prospectively recorded and less likely to be impacted by recall or self-report bias.

In contrast to the results from the NLCS that showed an increase in CRC risk only among women, our work showed similar risk in both males and females. We found that the OR in males appeared lower in younger versus older males. This age difference might provide a possible explanation for the inconsistency of our results compared to the NLCS, since the mean age for males in the NLCS was 61 years compared to 71 in the current work.

Our study had several limitations. THIN database lacks information regarding pre malignant adenomas, tumor location and tumor stage. Previous works demonstrated conflicting results regarding the influence of tumor location on the association between height and CRC risk. While some works show higher association with colon compared to rectal cancers (26), other works demonstrated higher risk for distal compared to proximal colonic lesions (13). We were unable to evaluate this possible association in the current study due to lack of information. Considering other potential limitations, our study suffered from missing data. For example, information regarding height was missing for 11,012 cases, thus, the analysis was restricted among subjects with height information. However, there is no reason to assume differential recording of height based on height or CRC status. The THIN database also lack information regarding other known CRC risk factors such as diet composition and physical activity. Finally the current work did not evaluate any specific biological mechanism that could explain the elevated risk, although several biologically plausible pathways were previously described.

In summary, we have shown that increasing height is an independent risk factor for CRC in both men and women. Major risk scores for CRC currently do not include height as part of their nomogram (34), and only one model in the Korean population include height as a risk factor in women (35). If confirmed, height should be included in future risk score models for both sexes.

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Dr. Yang and Dr. Boursi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Yang YX, Boursi B, Haynes K and Mamtani R contributed to conception and design of the study; Yang YX and Boursi B acquired the data; Yang YX, Boursi B, Haynes K and Mamtani R contributed to analysis and interpretation of data, drafting the article or revising it critically for important intellectual content; and final approval of the version to be published.

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¹ Of them 11,012 CRC cases.

Figure 1.
Patient Selection flowchart

Table 1

Characteristics of cases and controls

	Cases (n=9,978)	Controls (n=26,847)	Unadjusted OR (95% CI)	P-value
Age at index date (year SD)	71.8 (10.6)	71.7 (10.5)	NA	NA
Male sex (% SD)	56.3% (0.5)	56.3% (0.5)	NA	NA
Duration of follow-up before index date (years SD)	8.1 (3.9)	7.8 (3.9)	NA	NA
Diabetes mellitus (% SD)	17.3% (0.4)	15.0% (0.4)	1.16 (1.09-1.24)	<0.0001
BMI >30 (% SD)	32.9% (0.5)	31.2% (0.5)	1.10 (1.04-1.16)	<0.0001
BMI >40 (% SD)	3.2% (0.2)	2.6% (0.2)	1.25 (1.09-1.44)	0.001
Smoking (ever) (% SD)	62.3% (0.5)	58.8% (0.5)	1.20 (1.14-1.26)	<0.0001
Current smokers (% SD)	10.5% (0.3)	10.7% (0.3)	1.02 (0.94-1.11)	0.61
Alcohol use (% SD)	78.6% (0.4)	78.2% (0.5)	1.07 (1.00-1.14)	0.05
Alcoholism (% SD)	0.9% (0.09)	0.6% (0.07)	1.54 (1.19-2.00)	0.001
Chronic NSAIDs/Aspirin use (% SD) ^{\$}	37.8% (0.5)	39.5% (0.5)	0.95 (0.90-1.00)	0.05
Previous screening colonoscopy (% SD) ^I	2.0% (0.1)	2.7% (0.2)	0.79 (0.67-0.93)	0.005

^{\$}First Prescription at least 12 month before index date and last prescription within 6 months before index date, cumulative duration of therapy more than 365 days.

^I more than two years before index date.

Table 2

multivariable analysis of CRC risk by height quartiles in males and females

Height quartiles ²	Males			
	Case (5,617) N (%)	Control (15,122) N (%)	Unadjusted OR (95%CI, p-value)	Adjusted OR ¹ (95%CI, p-value)
Q1	1,366 (24.3%)	3,966 (26.2%)	Ref.	Ref.
Q2	1,504 (26.8%)	4,018 (26.6%)	1.12 (1.03-1.22, 0.01)	1.11 (1.02-1.22, 0.02)
Q3	1,236 (22.0%)	3,474 (23.0%)	1.09 (0.99-1.19, 0.08)	1.08 (0.98-1.19, 0.1)
Q4	1,511 (26.9%)	3,664 (24.2%)	1.26 (1.15-1.38, <0.0001)	1.25 (1.14-1.37, <0.0001)
Per 10cm increase in height	5,617	15,122	1.10 (1.05-1.15, <0.0001)	1.10 (1.05-1.15, <0.0001)

Height quartiles	Females			
	Case (4,361) N (%)	Control (11,725) N (%)	Unadjusted OR (95%CI, p-value)	Adjusted OR ¹ (95%CI, p-value)
Q1	1,058 (24.3%)	3,132 (26.7%)	Ref.	Ref.
Q2	1,111 (25.5%)	3,147 (26.8%)	1.08 (0.97-1.19, 0.15)	1.08 (0.97-1.19, 0.15)
Q3	1,061 (24.3%)	2,573 (21.9%)	1.29 (1.16-1.43, <0.0001)	1.28 (1.15-1.42, <0.0001)
Q4	1,131 (25.9%)	2,873 (24.5%)	1.25 (1.13-1.39, <0.0001)	1.25 (1.12-1.39, <0.0001)
Per 10cm increase in height	4,361	11,725	1.17 (1.10-1.23, <0.0001)	1.16 (1.10-1.23, <0.0001)

¹ Adjusted to diabetes mellitus, ischemic heart disease, connective tissue diseases, BMI, smoking history alcohol consumption, chronic use of Aspirin/NSAIDs, and performance of screening colonoscopy

² For males: Q1 – height<170cm; Q2 – 170-175cm; Q3 – 175-179cm; Q4 – height>179cm. For females: Q1 – height<156cm; Q2 – 156-160cm; Q3 – 160-165cm; Q4 – height>165cm.

Table 3

multivariable analysis of CRC risk by height quartiles and 10cm increase in height, in males < and > than 60

Males<60				
Height quartiles²	Case (856) N (%)	Control (2,169) N (%)	Unadjusted OR (95%CI, p-value)	Adjusted OR¹ (95%CI, p-value)
Q1	151 (17.6%)	393 (18.1%)	Ref.	Ref.
Q2	208 (24.3%)	521 (24.0%)	1.05 (0.82-1.34, 0.72)	1.04 (0.81-1.34, 0.75)
Q3	184 (21.5%)	529 (24.4%)	0.93 (0.72-1.21, 0.6)	0.95 (0.73-1.23, 0.69)
Q4	313 (36.6%)	726 (33.5%)	1.15 (0.91-1.46, 0.24)	1.16 (0.91-1.48, 0.22)
Per 10cm increase	856	2,169	1.05 (0.94-1.18, 0.39)	1.06 (0.94-1.19, 0.35)

Males>60				
Height quartiles	Case (4,761) N (%)	Control (12,953) N (%)	Unadjusted OR (95%CI, p-value)	Adjusted OR¹ (95%CI, p-value)
Q1	1,215 (25.5%)	3,573 (27.6%)	Ref.	Ref.
Q2	1,296 (27.2%)	3,497 (27.0%)	1.13 (1.03-1.24, 0.01)	1.12 (1.02-1.24, 0.02)
Q3	1,052 (22.1%)	2,945 (22.7%)	1.11 (1.01-1.23, 0.04)	1.11 (1.00-1.22, 0.05)
Q4	1,198 (25.2%)	2,938 (22.7%)	1.28 (1.16-1.41, <0.0001)	1.26 (1.15-1.4, <0.0001)
Per 10cm increase	4,761	12,953	1.11 (1.05-1.17, <0.0001)	1.10 (1.05-1.16, <0.0001)

¹ Adjusted to diabetes mellitus, ischemic heart disease, connective tissue diseases, BMI, smoking history, alcohol consumption, chronic use of Aspirin/NSAIDs, and performance of screening colonoscopy

² For males: Q1 – height<170cm; Q2 – 170-175cm; Q3 – 175-179cm; Q4 – height>179cm. For females: Q1 – height<156cm; Q2 – 156-160cm; Q3 – 160-165cm; Q4 – height>165cm.

Table 4

multivariable analysis of CRC risk by height quartiles and 10cm increase in height, in females < and > than 60

Females<60				
Height quartiles²	Case (170) N (%)	Control (457) N (%)	Unadjusted OR (95%CI, p-value)	Adjusted OR¹ (95%CI, p-value)
Q1	105 (15.6%)	331 (18.4%)	Ref.	Ref.
Q2	152 (22.6%)	426 (23.8%)	1.18 (0.88-1.58, 0.27)	1.16 (0.86-1.57, 0.32)
Q3	170 (25.3%)	421 (23.5%)	1.33 (1.00-1.79, 0.05)	1.34 (1.00-1.8, 0.05)
Q4	245 (36.5%)	616 (34.3%)	1.29 (0.98-1.7, 0.07)	1.3 (0.98-1.71, 0.07)
Per 10cm increase	170	457	1.18 (1.03-1.36, 0.02)	1.19 (1.04-1.37, 0.01)

Females>60				
Height quartiles	Case (3,689) N (%)	Control (9,931) N (%)	Unadjusted OR (95%CI, p-value)	Adjusted OR¹ (95%CI, p-value)
Q1	953 (25.8%)	2,801 (28.2%)	Ref.	Ref.
Q2	959 (26.0%)	2,721 (27.4%)	1.06 (0.96-1.18, 0.26)	1.06 (0.96-1.19, 0.25)
Q3	891 (24.2%)	2,152 (21.7%)	1.28 (1.15-1.43, <0.0001)	1.27 (1.14-1.42, 0.001)
Q4	886 (24.0%)	2,257 (22.7%)	1.25 (1.12-1.4, <0.0001)	1.25 (1.11-1.4, <0.0001)
Per 10cm increase	3,689	9,931	1.16 (1.10-1.23, <0.0001)	1.16 (1.09-1.23, <0.0001)

¹ Adjusted to diabetes mellitus, ischemic heart disease, connective tissue diseases, BMI, smoking history, alcohol consumption, chronic use of Aspirin/NSAIDs, and performance of screening colonoscopy

² For males: Q1 – height<170cm; Q2 – 170-175cm; Q3 – 175-179cm; Q4 – height>179cm. For females: Q1 – height<156cm; Q2 – 156-160cm; Q3 – 160-165cm; Q4 – height>165cm.