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BRIEF REPORT

Association between greater leg length and increased incidence of colorectal cancer: the atherosclerosis risk in communities (ARIC) study

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Abstract

Purpose Previous studies have reported that taller people have an increased risk of colorectal cancer (CRC). We examined the association of two height components—leg length and sitting height—with CRC risk in 14,532 individuals aged 45–64 years in the Atherosclerosis Risk in Communities study.

Methods Anthropometrics were measured at baseline (1987–1989). Incident CRC cases ($n = 382$) were ascertained from 1987 to 2012. Cox proportional hazards regression was used to estimate multivariable-adjusted hazard ratios for CRC and colon cancer across quintiles of sex-specific leg length and sitting height.

Results The highest (versus the lowest) quintile of leg length was associated with a 36% greater CRC risk (p-trend = 0.04), and 51% greater colon cancer risk (p-trend = 0.01). For the top four quintiles combined, risk was increased by 34% for CRC and by 45% for colon cancer versus the lowest quintile. Total height and sitting height were not significantly associated with CRC or colon cancer risk. A small number of cases ($n = 57$) limited our ability to conduct subgroup analyses for rectal cancer.

Conclusions A positive association of leg length with CRC and colon cancer risk suggests that biological mechanisms leading to greater leg length during puberty may explain the association between taller height and CRC.

Keywords Colorectal cancer · Leg length · ARIC · Prospective cohort · Risk

Introduction

Several epidemiological studies have found an association between taller height and increased colorectal cancer (CRC) risk [1–4]. Possible physiologic explanations involve factors that jointly influence attained height and CRC risk, and likely include (1) a larger pool of at-risk colonic cells among taller individuals [5], and/or (2) a greater exposure to a high caloric diet [6, 7] and growth hormones such as insulin-like growth factor-1 (IGF-1) in early life [8, 9]. Exposures in early life may influence future CRC risk, or they may be correlated with later life factors that are then associated with CRC risk [8].

Although many studies have examined associations between total height and CRC risk, few have investigated associations of height components—leg length or sitting height—with CRC risk [7]. Given that leg length and sitting height represent distinct growth periods at the physiologic level [7, 10, 11], assessing their individual associations with CRC risk may provide insights into mechanisms

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of the association between height and CRC. Leg length reflects a peak growth earlier during the pubertal growth spurt, whereas sitting height is associated with later growth in puberty and may be a marker for factors acting in this period, or it could reflect higher number of colonic cells [9, 12, 13]. It has been suggested that factors acting in the pre-pubertal period may be particularly important in determining future CRC risk [9, 12]. Therefore, our primary hypothesis was that leg length is the component of height most strongly associated with CRC risk. In addition, we were interested in examining the association between sitting height and colon cancer, because greater sitting height reflects an increased number of colonic cells and therefore may contribute to increased risk of colon and CRC cancer. To address these hypotheses, we evaluated the association of leg length and sitting height with CRC and colon cancer risk in the atherosclerosis risk in communities (ARIC) study, a large prospective cohort of mostly white and African-American participants.

Materials and methods

Study design

The ARIC study is a multi-center community-based prospective cohort study designed to investigate the etiology and natural history of atherosclerosis in middle-aged adults. Participants were recruited from four U.S. communities: Forsyth County, NC; Jackson, MS; suburbs of Minneapolis, MN; and Washington County, MD. The cohort included 15,792 participants aged 45–64 years who attended Visit 1 (baseline) in 1987–1989 [14]. The baseline and five follow-up visits (in 1990–1992, 1993–1995, 1996–1998, 2011–2013, and 2016–2017) included interviews, laboratory measurements, and clinical examinations. The ARIC study protocol was approved by the Institutional Review Board of each participating study center, and informed consent was obtained from each study participant.

Participants were excluded from this analysis if their self-reported race was other than white or African-American ($n=48$), or if they did not consent to studies of non-cardiovascular disease ($n=187$), had a history of cancer at baseline ($n=882$), or had missing data for total height ($n=22$), or seated height ($n=27$), or other covariates ($n=96$). The final analytic sample included 14,532 participants.

Exposure and covariate assessment

Information on age, sex, race, educational attainment, smoking history, alcohol consumption, physical activity, and aspirin intake during the last 2 weeks was collected in an interview at Visit 1. Participants were defined as having diabetes if they self-reported physician diagnosis or treatment for diabetes, had a fasting glucose ≥ 126 mg/dL, or a non-fasting glucose ≥ 140 mg/dL at Visit 1. Dietary information was assessed using a 66-item slightly modified version of the Harvard food frequency questionnaire [15] at visit 1. Trained technicians took anthropometric measurements for participants dressed in light clothing and without shoes. Standing height was measured to the nearest centimeter using a wall-mounted ruler. Sitting height was measured to the nearest centimeter with the participant seated on a stool against a wall-mounted ruler. Sitting height was estimated as seated height minus stool height, and leg length was estimated as standing height minus sitting height. Weight was measured using a balance scale. Waist (umbilicus) and hip (maximum buttocks) circumferences were measured using a flexible tape, to the nearest cm, with the participant standing. Waist-to-hip ratio was calculated as waist measurement divided by hip measurement [16].

Cancer assessment

CRC incidence was ascertained from 1987 through 2012 using state cancer registries in Minnesota, North Carolina, Maryland, and Mississippi, and supplemented by abstraction of medical records and hospital discharge summaries [14]. All records with ICD codes indicating possible colon and rectal cancer diagnosis (ICD-O-1: 153.0–153.4, 153.6–153.8, 154.0–154.1; ICD-O-2 and ICD-O-3: 18.0, 18.2–18.9, 19.9, 20.9; ICD-8 & 9: 153.0–153.4, 153.6–153.8, 154.0–154.1; ICD-10: 18.0, 18.2–18.9, 19.9, 20.9) were included [14].

In addition, participants who had self-reported a diagnosis of cancer on an ARIC annual or semi-annual follow-up telephone call were contacted separately for more information on cancer diagnoses, and medical records pertaining to cancer diagnoses and treatment were collected. Primary site, date of cancer diagnosis, and source of diagnostic information were recorded. Persons with cancer-related hospitalizations that were not previously identified as cases by linkage with state cancer registries were included as cases after medical records were obtained and abstracted to confirm the diagnosis of cancer [14]. A total of 382 CRC cases, 196 in men and 186 in women, were ascertained over a maximum follow-up of 26.1 years, with a median follow-up time of 23.2 years. We additionally examined the association of leg length and sitting height with colon cancer risk ($n=325$). The number of rectal cancer cases was too low to study separately ($n=57$).

Statistical analysis

Sex-specific quintile cut-points were generated for total height, leg length, and sitting height, because of their

different ranges in men and women. Sex- and race-specific Pearson correlation coefficients were computed to estimate correlations between leg length, sitting height, and height. We used Cox proportional hazards regression to estimate CRC and colon cancer risk associated with quintiles of height, leg length and sitting height, using the lowest (shortest) quintile as the reference level. Test of the linear trend across the quintiles were conducted by including the quintiles in the models as a continuous term. In addition, we also calculated HRs for the four highest quintiles compared to the lowest quintile in a post hoc analysis, as it appeared that the association was most striking for this contrast.

In Model 1, we adjusted for age, sex, race, and study center. In Model 2, we further adjusted for other demographic and environmental risk factors associated with CRC including smoking status, alcohol consumption, education level, physical activity, waist-to-hip ratio, diabetes, and female hormone replacement therapy (HRT) use. To adjust for HRT, we entered into the model terms designating female-HRT use, female-no HRT use, and male. Interactions of leg length and sitting height, with sex, race, and age (cut-point at median) were evaluated by including the cross-product term in the models. The proportional hazards assumption was tested by examining whether the ln (-ln) survival curves for the height and its components were parallel, respectively. There was no evidence of violation.

To address potential residual confounding by known dietary risk factors for CRC in Model 3, we created a 5-item dietary score including intakes of sugar-sweetened beverages (0 g/day, ≥ 0–< 250 g/day, ≥ 250 g/day); fruits and vegetables (≥ 5 servings/day, ≥ 3–< 5 servings/day, < 3 servings/day); fiber (≥ 25 g/day, 12.5–< 25 g/day, < 12.5 g/day); red and processed (RP) meats (< 500 g/week RP and < 3 g/day P, < 500 g/week RP and 3–< 50 g/day P, ≥ 500 g/week RP or ≥ 50 g/day P); and alcohol (men: ≤ 20, > 20–30, and > 30 g/day; women: ≤ 10, > 10–20, and > 20 g/day) based on the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) prevention guidelines [17]. Each recommendation contributed 1, 0.5, or 0 points to the adherence score, indicating full adherence, partial adherence, and no adherence, respectively. Cut-points for sugar-sweetened beverages, fruits and vegetables, fiber, red and processed meats, and alcohol were chosen to match those in other studies to maintain comparability [18–20].

To examine the association of leg length and sitting height with CRC risk independent from total height, we regressed leg length and sitting height on total height, race, and sex, and then entered the residuals into Cox regression models adjusted for all variables in Model 3 except race and sex (residuals model). All analyses were implemented using SAS version 9.4. All tests were two-sided, and a p value < 0.05 was considered to be statistically significant.

Results

At baseline, the 14,532 participants were, on average, 54 years old, 45% were male, and 25% were African-American. In men, the mean (SD) leg length was 84.0 (4.6) cm and mean (SD) height was 176.0 (6.6) cm. In women, the mean (SD) leg length was 76.6 (4.2) cm and the mean (SD) height was 162.2 (6.0) cm. Participants with longer legs tended to be taller, African-American, male, heavier, and more likely to be educated beyond high school (Supplemental Table 1). Similar trends were observed for sitting height (Supplementary Table 2).

Leg length, sitting height, and height were positively correlated (all $p < 0.0001$).The correlation between leg length and total height (men: $r = 0.83$; women: $r = 0.81$; sexes combined $r = 0.82$) and between sitting height and total height (men: $r = 0.69$; women: $r = 0.71$, combined $r = 0.71$) were stronger than the correlation between leg length and sitting height (men: $r = 0.15$; women: $r = 0.21$; combined $r = 0.19$).

After adjusting for age, sex, race, field center, demographic, environmental and dietary risk factors (Model 3), the HRs (95% CI) for each quintile of height were [$Q1$: 1 (reference), $Q2$: 0.92 (0.66–1.29), $Q3$: 1.24 (0.91–1.70), $Q4$: 1.07 (0.78–1.48), and $Q5$: 1.12 (0.80–1.57), p-trend = 0.46]. The associations with colon cancer followed a similar pattern, and the HRs for each quintile were [$Q1$: 1 (reference), $Q2$: 1.01 (0.70–1.46), $Q3$: 1.34 (0.94–1.89), $Q4$: 1.16 (0.81–1.65), and $Q5$: 1.28 (0.89–1.84), p-trend = 0.37].

Associations of leg length and sitting height with CRC risk

After adjusting for age, sex, race, and field center (Model 1), demographic and environmental risk factors (Model 2), and known dietary risk factor (Model 3), greater leg length was associated with higher CRC risk. CRC risk was similarly increased in each of the top four quintiles [$Q1$: (reference), $Q2$: 1.51, $Q3$: 1.28, $Q4$: 1.35, and $Q5$: 1.36; p-trend = 0.04 (Model 3)] and when the top four quintiles were combined, the HR of CRC was 1.34 (95% CI 1.01–1.78), compared to the lowest quintile. In the residuals model, those in the top quintile had a 1.43 times higher CRC risk (95% CI 1.06–1.92) compared to the bottom quintile (p-trend = 0.02) (Table 1). The association between leg length and CRC risk

Table 1 Association of baseline leg length and sitting height quintiles with incident colorectal and colon cancer risk, ARIC study, 1987–2012

	Overall	*Q*1*	*Q*2*	*Q*3*	*Q*4*	*Q*5*	*Q*2–*Q*5 versus *Q*1	*p*-trend
Hazard ratios for CRC (95% CI)								
Leg length								
Number of cases	382	61	87	68	87	79	382	
Person years		53,763	59,492	50,392	61,891	53,528	279,066	
Model 1[a]		1 (ref)	1.42 (1.02–1.97)	1.26 (0.89–1.78)	1.29 (0.92–1.80)	1.29 (0.91–1.83)	1.32 (1.00–1.75)	0.05
Model 2[b]		1 (ref)	1.51 (1.08–2.10)	1.29 (0.90–1.83)	1.35 (0.96–1.90)	1.36 (0.95–1.96)	1.38 (1.04–1.84)	0.03
Model 3[c]		1 (ref)	1.51 (1.08–2.10)	1.28 (0.90–1.83)	1.35 (0.96–1.89)	1.36 (0.95–1.95)	1.34 (1.01–1.78)	0.04
Residuals model[c]		1 (ref)	1.49 (1.07–2.09)	1.31 (0.91–1.88)	1.42 (0.99–2.03)	1.50 (1.00–2.25)	1.43 (1.06–1.92)	0.02
Sitting height								
Number of cases	382	64	77	107	63	71	382	
Person years		43,428	60,950	65,665	54,533	54,490	279,066	
Model 1[a]		1 (ref)	0.90 (0.64–1.25)	1.30 (0.95–1.79)	1.00 (0.69–1.42)	1.26 (0.88–1.80)	1.10 (0.83–1.45)	0.46
Model 2[b]		1 (ref)	0.88 (0.62–1.24)	1.29 (0.93–1.79)	0.98 (0.68–1.42)	1.21 (0.83–1.75)	1.07 (0.80–1.43)	0.57
Model 3[c]		1 (ref)	0.89 (0.63–1.25)	1.31 (0.94–1.81)	0.99 (0.68–1.43)	1.21 (0.84–1.76)	1.10 (0.83–1.47)	0.57
Residuals model[c]		1 (ref)	0.91 (0.64–1.29)	1.35 (0.95–1.92)	1.03 (0.69–1.55)	1.29 (0.84–1.99)	1.07 (0.78–1.46)	0.45
Hazard ratios for Colon Cancer (95% CI)								
Leg length								
Number of cases	325	48	69	60	78	70	325	
Person years		53,763	59,492	50,392	61,891	53,528	279,066	
Model 1[a]		1 (ref)	1.42 (0.98–2.05)	1.40 (0.95–2.05)	1.44 (1.00–2.08)	1.42 (0.97–2.08)	1.42 (1.04–1.95)	0.03
Model 2[b]		1 (ref)	1.51 (1.04–2.20)	1.45 (0.98–2.13)	1.54 (1.06–2.23)	1.52 (1.02–2.25)	1.51 (1.10–2.07)	0.01
Model 3[c]		1 (ref)	1.51 (1.04–2.20)	1.45 (0.98–2.13)	1.53 (1.06–2.22)	1.51 (1.02–2.24)	1.45 (1.06–1.99)	0.01
Residuals model[d]		1 (ref)	1.49 (1.02–2.17)	1.45 (0.98–2.16)	1.59 (1.07–2.35)	1.63 (1.05–2.53)	1.51 (1.09–2.11)	0.01
Sitting height								
Number of cases	325	51	68	94	52	60	325	
Person years		43,428	60,950	65,665	54,533	54,490	279,066	
Model 1[a]		1 (ref)	1.00 (0.69–1.44)	1.44 (1.01–2.05)	1.03 (0.69–1.54)	1.32 (0.89–1.97)	1.19 (0.87–1.63)	0.26
Model 2[b]		1 (ref)	0.99 (0.68–1.44)	1.44 (1.00–2.06)	1.04 (0.69–1.57)	1.28 (0.85–1.92)	1.17 (0.85–1.62)	0.32
Model 3[c]		1 (ref)	1.00 (0.68 -1.45)	1.44 (1.00–2.06)	1.04 (0.69–1.57)	1.28 (0.85–1.93)	1.20 (0.87–1.66)	0.32
Residuals model[d]		1 (ref)	1.04 (0.71–1.53)	1.56 (1.06–2.28)	1.16 (0.74–1.81)	1.47 (0.92–2.37)	1.22 (0.87–1.72)	0.16

*Sex-specific leg length and sitting height were computed and recombined

**The contrast for the top 4 quintiles compared to the bottom quintile was calculated in a post hoc analysis

[a]Model 1 was adjusted for age, sex, race, and study center

[b]Model 2 was adjusted for age, sex, race, study center, smoking, alcohol consumption, education, physical activity, waist-to-hip ratio, diabetes and a 3-level variable indicative of sex and hormone replacement therapy (men, women on therapy, women no therapy)

[c]Model 3 was adjusted for age, sex, race, study center, smoking, alcohol consumption, education, physical activity, waist-to-hip ratio, diabetes, a 3-level variable indicative of sex and hormone replacement therapy (men, women on therapy, women no therapy), as well as dietary score based on of sugar-sweetened beverages, fruits and vegetables, fiber, red and processed meats and alcohol

[d]This model was adjusted for age, study center, smoking, alcohol consumption, education, physical activity, waist-to-hip ratio, diabetes, a 3-level variable indicative of sex and hormone replacement therapy (men, women on therapy, women no therapy) as well as dietary score based on of sugar-sweetened beverages, fruits and vegetables, fiber, red and processed meats and alcohol and the residuals of leg length regressed on height, sex, and race

[e]This model was adjusted for age, study center, smoking, alcohol consumption, education, physical activity, waist-to-hip ratio, diabetes, a 3-level variable indicative of sex and hormone replacement therapy (men, women on therapy, women no therapy) as well as dietary score based on of sugar-sweetened beverages, fruits and vegetables, fiber, red and processed meats and alcohol and the residuals of sitting height regressed on height, sex, and race

was generally similar in men and women, in whites and African Americans, and in older (> 54 years of age at baseline) and younger participants (Supplemental Table 3).

In contrast to leg length, sitting height was not associated with CRC risk (Table 1), in Models 1, 2, and 3, or after taking into account the correlation between sitting

height and height in the residuals model [*Q*1: 1 (reference), *Q*2: 0.91, *Q*3: 1.35, *Q*4: 1.03, *Q*5: 1.29, *p*-trend = 0.45].

Associations of leg length and sitting height with colon cancer risk

Associations of leg length and sitting height with colon cancer risk followed patterns similar to CRC risk. After multivariable adjustment (Model 3), each of the top four quintiles of leg length were associated with greater risk of colon cancer: HRs were 1.51, 1.45, 1.54, and 1.51 for *Q*2, *Q*3, *Q*4, and *Q*5, respectively, versus *Q*1 (*p*-trend = 0.01) and when the top four quintiles were combined, the HR of colon cancer was 1.45 (95% CI 1.06–1.99) and these associations persisted in the residuals model (Table 1). However, the associations between leg length and colon cancer risk did not differ in by sex, race or age (Supplemental Table 4, all *p*-interaction > 0.10). In parallel with CRC, the quintiles of sitting height were not consistently associated with colon cancer risk, in either Models 1, 2, 3 or after accounting for the correlation between sitting height and height (Table 1).

Discussion

In this prospective cohort study with a maximum of 26 years of follow-up, the highest (versus the lowest) quintile of leg length was associated with a 36% greater CRC risk, and 51% greater colon cancer risk. Notably, participants with longer legs (above the bottom 20th percentile) had an increased risk of CRC (by 34%), and of colon cancer (by 45%), compared to those with shorter legs (below the bottom 20th percentile). This association was independent of total height, and was similar across sex, race, and age. In contrast, sitting height was not consistently associated with CRC or colon cancer risk.

Although we did not find a statistically significant association, our results suggested an association between greater total height and increased CRC and colon cancer risk. The HRs were 12% greater and 27% greater for the fifth (tallest) versus the first (shortest) quintile, for CRC and colon cancer respectively. Our estimates are similar to previous findings that each 10-cm increase in height was associated with a 8–12% increase in CRC risk [3, 4]. Our post hoc power analysis indicated that we had approximately 71% power to detect a 12% or higher increased CRC risk for the fifth (tallest) versus first (shortest) quintile, which could explain the lack of association in our study.

Prior findings on the association between height components, CRC and colon cancer risk have been inconsistent [7]. Our findings for leg length measured in adulthood are compatible with those of the Boyd Orr cohort of 1167 white participants, which reported that one standard deviation increase in childhood leg length was associated with a 78% increase in CRC risk [21]. In contrast, the National Health and Nutrition Examination Study (NHANES) reported that being in the top versus bottom quartile of adult leg length was associated with a 40% increase in CRC risk [22] but a similar association was observed with sitting height and neither was statistically significant. In the Honolulu Heart Program of individuals of Japanese ancestry living in Hawaii, neither leg length nor sitting height was associated with CRC risk [23]. It is unclear whether the heterogeneity in results was due to differences in the populations of interest across studies, or chance variation. With regards to our findings for the sitting height-CRC association, post hoc power calculations indicated that our study had approximately 68% power to detect a 10% increase in CRC risk or larger between the fifth (longest) versus first (shortest) quintile. It is possible that limited power could explain the lack of association between height and CRC risk in our study.

Physiologically, the association between greater leg length and increased CRC risk may be explained by a greater exposure to dietary factors and endogenous growth hormones during the peak of leg length growth in early life [6, 7]. Greater nutrient consumption during early childhood causes long bone growth before and during puberty [24], which mainly contributes to longer legs rather than to greater sitting height [13]. Thus, compared to sitting height, leg length may be a better surrogate indicator for CRC risk factors involved in early life growth [11]. While we cannot rule out that the association between taller height and colon or CRC risk may be explained by a larger pool of colonic cells and greater sitting height in taller people, we did not find an association between greater sitting height and increased colon or CRC risk in this study.

Further, higher circulating levels of growth hormones, including IGF-1, influence cell proliferation, differentiation, and apoptosis through the IGF axis [25], which may in turn contribute to the development of future cancer [26, 27]. In line with this biological mechanism, most epidemiologic studies demonstrated that higher circulating levels of IGF-1 measured in mid and later life are associated with subsequent increased CRC risk [10, 26–29]. However, we did not measure circulating levels of biomarkers involved in the IGF pathway, but used leg length and sitting height as surrogate markers to evaluate the association. Thus we cannot conclude from our study whether early life exposures related to elevated IGF levels influence CRC risk directly or through mid to late life IGF levels [8]. Future studies evaluating early life and late life IGF circulating levels in combination with anthropomorphic measurements are needed to test whether the association between leg length and CRC is explained by circulating levels of IGF in early or mid and later life.

The strengths of this study include the prospective design, systematic CRC case validation, anthropometric measurements performed using standardized methods by

trained technicians, and the large, community-based sample of whites and African Americans. Although we cannot exclude the potential of residual confounding, the ARIC study provided detailed measurements of key covariates which allowed us to adjust for CRC risk factors in the analyses. Further, height and its components are determined early in life, and are therefore unlikely to be highly confounded by adult behaviors and characteristics associated with CRC development; although certain early life and later life risk factors can be correlated [24]. A limitation of the study is that leg length was not directly measured during primary data collection; instead, we calculated from standing height and sitting height measurements. Estimates of leg length may be affected by weight and body composition, due to variations in muscle and adipose tissue in the gluteal region of participants [16, 30]. These indirect measures could have resulted in the systematic underestimation of leg length for obese participants. However, we did not find appreciable changes in the effect estimates after adjusting for different measures of obesity, such as waist-to-hip ratio, body weight, and BMI. A final limitation is that various height components are highly correlated, and it is difficult to distinguish between the contributions of each component, although we used various statistical methods to determine their independent associations.

In summary, our findings of a differential association of CRC risk with leg length and sitting height corroborate the hypothesis that early life exposures are associated with future CRC risk. As leg length can be inexpensively measured in practice, future studies should be conducted to confirm its association with CRC risk and assess potential biological mechanisms, including measuring circulating IGF-1 levels across the lifecourse.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no potential conflicts of interest.

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