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Height as an Explanatory Factor for Sex Differences in Human Cancer

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Background Most cancers occur more frequently in men. Numerous explanations for this excess risk have been proposed, yet no study has quantified the degree to which height explains the sex difference even though greater height has been associated with increased risk for many cancers.

Methods During the period from 2000 to 2002, 65 308 volunteers aged 50 to 76 years were recruited to the Vitamins And Lifestyle (VITAL) study. Cancers of shared anatomic sites (n = 3466) were prospectively identified through 2009 through the Surveillance, Epidemiology, and End Results cancer registry. Age- and race-adjusted hazard ratios (HRs) for the associations between sex and incident cancers were estimated using Cox proportional hazards models, with and without adjustment for height and height squared as measures of body size.

Results Men had a 55% increased risk of cancer at shared sites (HR = 1.55; 95% confidence interval [CI] = 1.45 to 1.66). When height was accounted for, 33.8% (95% CI = 10.2% to 57.3%) of the excess risk for men was explained by the height differences between sexes. The proportion mediated by height was 90.9%, 57.3%, and 49.6% for kidney, melanoma, and hematologic malignancies, respectively, with little evidence that height mediates the sex difference for gastrointestinal tract, lung, and bladder cancers. For comparison, more than 35 lifestyle and medical risk factors only explained 23.1% of the sex difference in cancer risk at shared sites.

Conclusions Height is an important explanatory factor for the excess risk for men for many shared-site cancers. This suggests that some of the excess risk is due to factors associated with height (eg, number of susceptible cells in a specific organ or growth-influencing exposures in childhood).

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It is well established that the age-adjusted incidence of cancers of most shared anatomic sites is higher in men than women. As an example, Table 1 provides recent data from the US Surveillance, Epidemiology, and End Results (SEER) cancer registry (1) that shows a 28% to 63% higher risk of invasive cancer for shared sites overall and most cancer sites for men; notable exceptions are urinary system cancers, for which men have a threefold higher risk than women, and thyroid cancer, for which women have a greater risk than men (1). Although not fully understood, mechanisms proposed to underlie the male predominance include differences in lifestyle factors, occupational exposures, and sex hormone levels (2–7).

A second recurrent association in prospective studies—observed for boths sexes and for many cancer sites (8–22)—is that between height and incidence of human cancer. Several factors have been suspected to contribute to this association, but the exact biologic mechanisms remain elusive. For cancers that have been associated with height, the incidence has been 20% to 60% higher among persons in the top height categories (8). As men are, on average, approximately 5.5 inches (approximately 14 cm) taller than women (23), we sought to investigate with data from the prospective Vitamins And Lifestyle (VITAL) study whether and to what degree height accounts for sex differences in human cancers (ie, whether height is a mediating or explanatory factor). To our knowledge, this is the first study to examine this hypothesis.

Methods

Study Cohort

The VITAL study (24) was approved by the institutional review board of the Fred Hutchinson Cancer Research Center. The institutional review board considered that consent was given passively if the individual returned a completed questionnaire. During the period from 2000 to 2002, we mailed questionnaires to 364 418 men and women aged 50 to 76 years living in the area of Washington State covered by the SEER cancer registry; of these, 79 300 were returned, and 77 719 were eligible for participation. For this analysis, we excluded 11 249 participants with a prior history of cancer

Table 1. Age-adjusted incidence rates of invasive cancers by sex, Surveillance, Epidemiology, and End Results (SEER) cancer registry 2005–2009*

Cancer	Males	Females	Male/Female ratio
All shared sites†	365.7	229.6	1.59
Gastrointestinal tract	105.9	70.6	1.50
Colon and rectum	54.0	40.2	1.34
Pancreas	13.8	10.8	1.28
Lung and bronchus	76.4	52.7	1.45
Urinary system	59.0	20.0	2.95
Kidney and renal pelvis	20.7	10.5	1.97
Bladder	37.0	8.9	4.16
Melanoma	27.2	16.7	1.63
Thyroid	5.9	17.3	0.34
Hematologic malignancies	50.4	33.3	1.51

* Rates are given per 100 000 persons and are age-adjusted to the 2000 US standard population (19 age groups; Census P25-1130) from 18 SEER areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California [excluding San Francisco/San Jose-Monterey/Los Angeles], Kentucky, Louisiana, New Jersey, and Georgia [excluding Atlanta/Rural Georgia]) (1).

† Includes cancer of the oral cavity and pharynx, digestive system, respiratory system, bones and joints, soft tissue, urinary system, eye and orbit, brain and nervous system, and endocrine system, as well as melanoma of the skin, hematologic malignancies, Kaposi sarcoma, and mesothelioma; does not include ill-defined and unspecified cancers.

other than nonmelanoma skin cancer reported at baseline or missing (n = 214) cancer information at baseline and 1195 participants missing data on height. We additionally excluded 23 case subjects with postbaseline cancer on a death certificate only without a diagnosis date, leaving 65 038 participants for study.

Data Collection

A 24-page self-administered, sex-specific baseline questionnaire covered demographic factors, height and weight, medication use, diet, health history, family medical history, and cancer risk factors. Dietary factors were assessed from a 120-item food frequency questionnaire. Physical activity was measured in metabolic equivalent tasks-hours (MET-hours) based on a questionnaire detailing 13 types of recreational physical activity. Height was assessed by self-report of maximum height.

Case Ascertainment

Incident, invasive cancer cases other than nonmelanoma skin cancer were identified through December 31, 2009, by annual linkage to the western Washington SEER cancer registry (24). Cancers included as outcomes in this analysis were cancers at anatomic sites shared by men and women; we excluded reproductive-tract cancers as well as breast cancer, the latter because the female breast physiology differs substantially from the male physiology and the incidence varies by about two orders of magnitude between the sexes. Cancers were grouped by organ system or organ, and those with 90 or more cases were included in site-specific analyses.

Follow-up for Censoring

Excluding the 5.33% of the cohort with incident diagnoses of cancers from shared anatomic sites, the remaining participants were right-censored from the analysis at the earliest date of the following events: study withdrawal (0.03%), emigration from the SEER region (6.8%), diagnosis of breast or reproductive cancer in men and women (5.5%), diagnosis of cancer of unknown primary site (0.07%), death (3.7%), or last linkage to the SEER registry (78.9%). Moves out of the SEER region were identified by linkage to the US Post Office National Change of Address file, follow-up letters, and phone calls. Deaths were ascertained by linkage to the Washington State death file.

Statistical Analysis

We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between sex and risk of incident malignancies. In all regression models, age was the time metric, with participants entering at the age of completing the baseline questionnaire and exiting at their age at end of follow-up. The proportionality of hazards was verified by plotting the Schoenfeld residuals against the timeline. Model 1 included sex, adjusted for age and race only, whereas model 2 was additionally adjusted for height. Our goal was to control for height using parameters that accurately reflect the association between height and cancer. Because cancer arises primarily in cells that line body structures, the number of cells at risk may be proportional to a two-dimensional surface area; to account for this possibility, we parameterized height as height and height squared. Model 3 included sex, adjusted for age, race, and multiple potential factors that may explain the sex difference in cancer incidence other than height; these factors are listed in detail in the notes to Table 4. The covariables were selected a priori for inclusion in the analysis based on their association with cancer from published reviews [eg, references (25,26)] or the VITAL study. Model 4 included all of the factors in model 3 plus height and height squared. Mediation by height (ie, the relative contribution of height to the increased cancer incidence among men) was assessed by calculating the percentage change in the β coefficient for male sex between models 1 and 2 and between models 3 and 4. The 95% confidence intervals around percent change in β and two-sided *P* values were calculated for the hypothesis that the βs for sex in the models with and without height were equal by using the β estimate for sex from the model without height as an offset for the β in the model with height. All reported *P* values were two-sided, with *P* less than .05 considered statistically significant. All analyses were performed using SAS/STAT (SAS Institute Inc, Cary, NC).

Results

Overall, 32 144 men and 32 894 women with a mean age of 61.5 years (standard deviation [SD] = 7.4) were included in this study (Table 2). Men were more educated and heavier than women. Men also exercised more, consumed more alcohol, smoked more in their lifetime, and consumed more red meat and fewer servings of fruits and vegetables than women. As expected, men were taller than women (mean ± SD = 70.67 ± 2.76 vs 64.69 ± 2.64 inches [179.5 ± 7.0 vs 164.3 ± 6.7 cm]; $P < .001$).

After a mean follow-up of 7.3 ± 2.1 years, 3466 (5.3%) participants developed a cancer at a shared site other than breast. Table 3 provides the association of height with cancer outcomes, a prerequisite for mediation (27). After controlling for sex and race, height was statistically significantly associated with total shared-site cancer

Table 2. Characteristics of male and female Vitamins and Lifestyle (VITAL) cohort participants*

Characteristic	Males, No. (%) (n = 32 144)	Females, No. (%) (n = 32 894)
Age, y		
<55	7955 (24.75)	8368 (25.44)
55–59	7523 (23.40)	7897 (24.01)
60–64	6038 (18.78)	5817 (17.68)
65–69	5277 (16.42)	4932 (14.99)
≥70	5351 (16.65)	5880 (17.88)
Education		
≤High school graduate	4971 (15.51)	7547 (23.07)
Some college	11 203 (34.94)	13 589 (41.53)
≥College graduate	15 885 (49.55)	11 583 (35.40)
Race		
White	29 817 (93.13)	30 479 (93.08)
Black	401 (1.25)	408 (1.25)
Hispanic	277 (0.87)	298 (0.91)
Asian/Pacific Islander	804 (2.51)	905 (2.76)
Native American	472 (1.47)	490 (1.50)
Other race	245 (0.77)	165 (0.50)
Height, in		
<65	452 (1.41)	15 949 (48.49)
65–68	6400 (19.91)	14 788 (44.96)
69–71	13 052 (40.60)	1953 (5.94)
>71	12 240 (38.08)	204 (0.62)
Body mass index, kg/m^2		
<25	8673 (27.41)	12 932 (41.12)
25–29.9	15 399 (48.66)	10 573 (33.62)
≥30	7571 (23.93)	7944 (25.26)
Average physical activity over prior 10 years (MET-hours/week)		
None	4695 (14.80)	4750 (14.64)
<4.37	7251 (22.86)	10 889 (33.55)
4.38–13.65	8868 (27.96)	9487 (29.23)
>13.65	10 906 (34.38)	7327 (22.58)
Alcohol consumption at age 45, drinks/day		
0	5154 (16.51)	7583 (23.68)
<1	15 515 (49.69)	19 899 (62.14)
1–2	5089 (16.30)	2781 (8.68)
≥2	5467 (17.51)	1761 (5.50)
Smoking, pack-years		
Nonsmoker	12 622 (39.61)	18 537 (56.69)
≤7.5	4998 (15.68)	5288 (16.17)
7.6–22.5	4521 (14.19)	3445 (10.54)
22.6–37.5	4834 (15.17)	2870 (8.78)
>37.5	4892 (15.35)	2557 (7.82)
Fruit and vegetable consumption, servings/day		
≤2.03	9347 (31.33)	5,673 (18.91)
2.04–3.14	8095 (27.13)	6730 (22.43)
3.15–4.78	7276 (24.39)	7774 (25.91)
>4.78	5116 (17.15)	9824 (32.75)
Red meat consumption, servings/week		
≤2.12	5627 (18.86)	9661 (32.20)
2.13–4.12	6630 (22.22)	8030 (26.77)
4.13–6.92	7877 (26.40)	7014 (23.38)
>6.92	9700 (32.51)	5296 (17.65)

* MET = metabolic equivalent of task.

Table 3. Association between height and cancer risk, Vitamins and Lifestyle (VITAL) cohort (n = 65 038)*

Cancer site	Cases, No.	HR (95% CI) per 5 inches of height†	P‡
All shared-site cancers§,‖	3466	1.15 (1.08 to 1.23)	<.001
Gastrointestinal tract¶	940	1.10 (0.97 to 1.24)	.13
Colon and rectum	491	1.12 (0.94 to 1.32)	.20
Pancreas	164	1.42 (1.07 to 1.88)	.02
Lung	743	1.04 (0.90 to 1.19)	.62
Urinary system#	338	1.38 (1.14 to 1.68)	.001
Kidney	191	1.63 (1.27 to 2.10)	<.001
Bladder	123	1.01 (0.73 to 1.42)	.94
Melanoma	349	1.28 (1.05 to 1.55)	.01
Thyroid	95	1.07 (0.73 to 1.57)	.74
Hematologic malignancies	693	1.23 (1.07 to 1.41)	.004
Myeloid neoplasms	169	1.26 (0.95 to 1.67)	.12
CLL/SLL	112	1.09 (0.77 to 1.55)	.63
B-cell neoplasms other than CLL/SLL or plasma cell disorders	264	1.34 (1.07 to 1.68)	.01

* CI = confidence interval; CLL/SLL = chronic lymphocytic leukemia/small lymphocytic leukemia; HR = hazard ratio.

† Adjusted for age, sex, and race.

‡ Two-sided *P* values are provided for the associations between height (continuous, per 5 inch) for the association and cancer risk.

§ Includes cancers of the gastrointestinal tract, lung, urinary system, head and neck, connective tissue, brain, and endocrine system, as well as melanoma and hematologic malignancies.

‖ Major categories (cancers of the gastrointestinal tract, lung, and urinary system; melanoma; and hematologic malignancies) do not add up to 3466 cases because of exclusion of cancer sites with less than 90 cases.

¶ Besides cancers of colon/rectum and pancreas, contains cancers of esophagus, stomach, liver, small intestines, anus and anal canal, gall bladder, biliary tract, and other or ill-defined digestive organs.

Besides cancers of kidney and bladder, contains cancers of renal pelvis, ureter, and other/unspecified urinary organs.

risk (HR = 1.15; 95% CI = 1.08 to 1.23; per 5 inches of increased height) and risk of cancers of the pancreas, urinary system overall and kidney in particular, melanoma, and hematologic cancers overall and, in particular, some B-cell neoplasms (Table 3).

Consistent with SEER data (Table 1), male sex was associated with a statistically significantly 55% higher total shared-site cancer risk in age- and race-adjusted models (HR = 1.55; 95% CI = 1.45 to 1.66) (Table 4, model 1). This finding reflected a higher risk of cancers at most sites (ie, gastrointestinal tract, lung, urinary system, melanoma, and hematologic malignancies) and most of the specific cancer types within those organs systems. After adjustment for numerous (eg, >35 in the case of total shared cancer) potential explanatory factors, including known and suspected risk factors for various cancers (Table 4, model 3), hazard ratios for male sex were attenuated but male sex remained associated with a statistically significantly higher total shared-site cancer risk (HR = 1.39; 95% CI = 1.21 to 1.60) and increased risk for urinary system cancers, melanoma, and hematologic cancers and most of the specific cancer types within these categories. However, sex was no longer associated with lung and total gastrointestinal cancers.

To investigate whether and to what degree the height difference between sexes could explain the observed male dominance in risk of most shared-site cancers, we additionally adjusted models 1 and 3 for height and height squared as measures of body size (models 2 and 4). Table 4 gives the β values and hazard ratios for male sex from these models, as well as the percent reduction in β when explanatory factors were added to the models. Percent reduction in β is referred to as the proportion mediated (28) or explained by

Table 4. Association between male sex and cancer risk before and after adjustment for height, by anatomic site, Vitamin and Lifestyle (VITAL) cohort (n = 65 038)*

Cancer site	Model 1 Age and race adjusted†	Model 1A Age and race adjusted‡	Model 2 Age, race, and height adjusted§	Model 3 Age and covariable adjusted‖	Model 4 Age, covariable, and height adjusted§,‖
All shared-site cancers (n = 3466)¶, #					
β (95% CI), male vs female	0.44 (0.37 to 0.51)	0.43 (0.34 to 0.51)	0.29 (0.19 to 0.40)	0.33 (0.19 to 0.47)	0.18 (0.01 to 0.34)
% reduction (95% CI); *P* value, in β vs model 1 or 1A**			33.8 (10.2 to 57.3); *P* = .005	23.1 (−9.4 to 55.5); *P* = .16	59.2 (19.9 to 98.5); *P* = .003
% reduction (95% CI); *P* value, in β vs model 3**					47.0 (−4.1 to 98.0); *P* = .07
HR (95% CI); *P* value, male vs female††	1.55 (1.45 to 1.66); *P* < .001	1.54 (1.41 to 1.67); *P* < .001	1.34 (1.21 to 1.48); *P* < .001	1.39 (1.21 to 1.60); *P* < .001	1.19 (1.01 to 1.41); *P* = .04
Gastrointestinal tract (n = 940)‡‡					
β (95% CI), male vs female	0.33 (0.20 to 0.46)	0.29 (0.13 to 0.45)	0.25 (0.06 to 0.45)	0.16 (−0.10 to 0.39)	0.08 (−0.24 to 0.39)
% reduction (95% CI); *P* value, in β vs model 1 or 1A**			23.0 (−37.1 to 83.1); *P* = .45	45.5 (−43.7 to 134.7) *P* = .32	73.8 (−35.7 to 183.3) *P* = .19
% reduction (95% CI); *P* value, in β vs model 3**					51.9 (−149.1 to 252.9) to *P* = .61
HR (95% CI); *P* value, male vs female††	1.39 (1.22 to 1.58); *P* < .001	1.34 (1.14 to 1.57); *P* < .001	1.29 (1.06 to 1.56); *P* = .01	1.17 (0.90 to 1.52); *P* = .23	1.08 (0.79 to 1.48); *P* = .64
Colon and rectum (n = 491)					
β (95% CI), male vs female	0.16 (−0.02 to 0.34)	0.18 (−0.05 to 0.40)	0.03 (−0.23 to 0.30)	0.25 (−0.11 to 0.60)	0.21 (−0.23 to 0.65)
% reduction (95% CI); *P* value, in β vs model 1 or 1A**			78.6 (−90.3 to 247.5); *P* = .36	<0; *P* = .70	<0; *P* = .89
% reduction (95% CI); *P* value, in β vs model 3**					15.7 (−160.6 to 192.0); *P* = .86
HR (95% CI); *P* value, male vs female††	1.17 (0.98 to 1.40); *P* = .08	1.20 (0.95 to 1.50); *P* = .12	1.04 (0.79 to 1.35); *P* = .80	1.28 (0.90 to 1.83); *P* = .17	1.23 (0.80 to 1.91); *P* = .35
Pancreas (n = 164)					
β (95% CI), male vs female	0.17 (−0.14 to 0.47)	0.08 (−0.30 to 0.46)	−0.15 (−0.62 to 0.31)	−0.43 (−1.05 to 0.19)	−0.67 (−1.42 to 0.09)
% reduction (95% CI); *P* value, in β vs model 1 or 1A**			192.8 (−88.2 to 473.8); *P* = .18	NA; *P* = .10	NA; *P* = .05
% reduction (95% CI); *P* value, in β vs model 3**					<0; *P* = .54
HR (95% CI); *P* value, male vs female††	1.18 (0.87 to1.60); *P* = .29	1.08 (0.74 to 1.58); *P* = .68	0.86 (0.54 to 1.37); *P* = .52	0.65 (0.35 to 1.21); *P* = .17	0.51 (0.24 to 1.09); *P* = .08
Lung (n = 743)§§					
β (95% CI), male vs female	0.36 (0.21 to 0.50)	0.29 (0.11 to 0.48)	0.36 (0.13 to 0.58)	0.03 (−0.21 to 0.27)	−0.01 (−0.32 to 0.31)
% reduction (95% CI); *P* value, in β vs model 1 or 1A**			1.1 (−60.6 to 62.8); *P* = .97	90.0 (7.9 to 172.2) to *P* = .03	102.7 (−5.7 to 211.2); *P* = .06
% reduction (95% CI); *P* value, in β vs model 3**					NA; *P* = .82
HR (95% CI); *P* value, male vs female††	1.43 (1.24 to 1.66); *P* < .001	1.34 (1.11 to 1.61); *P* = .002	1.43 (1.14 to 1.78); *P* = .002	1.03 (0.81 to 1.31); *P* = .81	0.99 (0.72 to 1.36); *P* = .96
Urinary system (n = 338)‖‖					
β (95% CI), male vs female	0.97 (0.73 to 1.20)	0.87 (0.58 to 1.16)	0.56 (0.21 to 0.91)	0.70 (0.34 to 1.06)	0.39 (−0.10 to 0.87)
% reduction (95% CI); *P* value, in β vs model 1 or 1A**			42.0 (5.5 to 78.5); *P* = .02	19.0 (−22.8 to 60.9); *P* = .37	55.5 (−0.1 to 111.1); *P* = .05
% reduction (95% CI); *P* value, in β vs model 3**					45.0 (−23.7 to 113.7); *P* = .20
HR (95% CI); *P* value, male vs female††	2.63 (2.08 to 3.33); *P* < .001	2.38 (1.78 to 3.18); *P* < .001	1.75 (1.23 to 2.49); *P* = .002	2.02 (1.40 to 2.90); *P* < .001	1.47 (0.91 to 2.38); *P* = .12

(Table continues)

Table 4. (Continued).

Cancer site	Model 1 Age and race adjusted†	Model 1A Age and race adjusted‡	Model 2 Age, race, and height adjusted§	Model 3 Age and covariable adjusted‖	Model 4 Age, covariable, and height adjusted§,‖
Kidney (n = 191)					
β (95% CI), male vs female	0.67 (0.37 to 0.97)	0.50 (0.14 to 0.86)	0.06 (−0.39 to 0.51)	0.46 (−0.01 to 0.92)	−0.04 (−0.65 to 0.57)
% reduction (95% CI); *P* value, in β vs model 1 or 1A**			90.9 (23.8 to 158.0); *P* = .008	9.3 (−83.2 to 101.9); *P* = .84	108.1 (−13.6 to 229.9); *P* = .08
% reduction (95% CI); *P* value, in β vs model 3**					109.0 (−25.3 to 243.2); *P* = .11
HR (95% CI); *P* value, male vs female††	1.95 (1.45 to 2.63); *P* < .001	1.66 (1.15 to 2.38); *P* = .006	1.06 (0.68 to 1.67); *P* = .79	1.58 (0.99 to 2.52); *P* = .06	0.96 (0.52 to 1.77); *P* = .90
Bladder (n = 123)					
β (95% CI), male vs female	1.74 (1.26 to 2.22)	1.72 (1.11 to 2.33)	1.78 (1.11 to 2.46)	1.37 (0.66 to 2.07)	1.55 (0.66 to 2.45)
% reduction (95% CI); *P* value, in β vs model 1 or 1A**			<0; *P* = .91	20.5 (−20.6 to 61.5); *P* = .33	9.4 (−42.9 to 61.8); *P* = .72
% reduction (95% CI); *P* value, in β vs model 3**					< ; *P* = .68
HR (95% CI); *P* value, male vs female††	5.70 (3.53 to 9.20); *P* < .001	5.56 (3.03 to 10.23); *P* < .001	5.94 (3.03 to 11.64); *P* < .001	3.91 (1.94 to 7.91); *P* < .001	4.73 (1.93 to 11.62); *P* < .001
Melanoma (n = 349)¶¶					
β (95% CI), male vs female	0.59 (0.38 to 0.81)	0.68 (0.41 to 0.94)	0.25 (−0.08 to 0.58)	0.77 (0.43 to 1.11)	0.32 (−0.13 to 0.77)
% reduction (95% CI); *P* value, in β vs model 1 or 1A**			57.3 (1.8 to 112.9); *P* = .04)	<0; *P* = .61	52.7 (−13.8 to 119.1); *P* = .12
% reduction (95% CI); *P* value, in β vs model 3**					58.2 (−0.5 to 116.9); *P* = .05
HR (95% CI); *P* value, male vs female††	1.81 (1.46 to 2.25); *P* < .001	1.97 (1.51 to 2.57); *P* < .001	1.29 (0.93 to 1.79); *P* = .13	2.16 (1.53 to 3.04); *P* < .001	1.38 (0.88 to 2.16); *P* = .16
Thyroid (n = 95)##					
β (95% CI), male vs female	−1.09 (−1.56 to −0.62)	−0.99 (−1.52 to −0.47)	−1.13 (−1.81 to −0.45)	−1.27 (−2.01 to −0.52)	−1.33 (−2.24 to −0.43)
% reduction (95% CI); *P* value, in β vs model 1 or 1A**			<0; *P* = .90	<0; *P* = .47	<0; *P* = .46
% reduction (95% CI); *P* value, in β vs model 3**					<0; *P* = .89
HR (95% CI); *P* value, male vs female††	0.34 (0.21 to 0.54); *P* < .001	0.37 (0.22 to 0.62); *P* < .001	0.32 (0.16 to 0.63); *P* = .001	0.28 (0.13 to 0.59); *P* = .001	0.26 (0.11 to 0.65); *P* = .004
Hematologic malignancies (n = 693)***					
β (95% CI), male vs female	0.49 (0.34 to 0.64)	0.49 (0.47 to 0.51)	0.25 (0.02 to 0.48)	0.53 (0.28 to 0.78)	0.34 (0.01 to 0.67)
% reduction (95% CI); *P* value, in β vs model 1 or 1A**			49.6 (2.4 to 96.8); *P* = .04	<0; *P* = .73	30.5 (−36.9 to 97.8); *P* = .38
% reduction (95% CI); *P* value, in β vs model 3**					36.2 (−25.5 to 98.0); *P* = .25
HR (95% CI); *P* value, male vs female††	1.63 (1.40 to 1.90); *P* < .001	1.63 (1.34 to 1.97); *P* < .001	1.28 (1.02 to 1.61); *P* = .04	1.70 (1.32 to 2.18); *P* < .001	1.40 (1.01 to 1.95); *P* = .04
Myeloid neoplasms (n = 169)					
β (95% CI), male vs female	0.73 (0.42–1.05)	0.70 (0.30 to 1.09)	0.37 (−0.11 to 0.84)	0.69 (0.18 to 1.20)	0.34 (−0.32 to 1.01)
% reduction (95% CI); *P* value, in β vs model 1 or 1A**			50.2 (−14.8 to 115.2); *P* = .13	1.0 (−71.9 to 73.9); *P* = .98	50.6 (−44.6 to 145.8); *P* = .30
% reduction (95% CI); *P* value, in β vs model 3**					50.1 (−46.1 to 146.2); *P* = .31
HR (95% CI); *P* value, male vs female††	2.08 (1.51 to 2.86); *P* < .001	2.01 (1.35 to 2.99); *P* < .001	1.44 (0.89 to 2.32); *P* = .13	1.99 (1.20 to 3.31); *P* = .008	1.41 (0.73 to 2.74); *P* = .31

(Table continues)

Table 4 (Continued).

Cancer site	Model 1 Age and race adjusted†	Model 1A Age and race adjusted‡	Model 2 Age, race, and height adjusted§	Model 3 Age and covariable adjusted‖	Model 4 Age, covariable, and height adjusted§,‖
CLL/SLL (n = 112)					
β (95% CI), male vs female	0.55 (0.16 to 0.93)	0.72 (0.20 to 1.23)	0.46 (−0.12 to 1.04)	0.78 (0.12 to 1.44)	0.74 (−0.13 to 1.60)
% reduction (95% CI); *P* value, in β vs model 1 or 1A**			15.6 (−91.2 to 122.4); *P* = .77	<0; *P* = .85	<0; *P* = .96
% reduction (95% CI); *P* value, in β vs model 3**					5.4 (−105.7 to 116.5); *P* = .92
HR (95% CI); *P* value, male vs female††	1.73 (1.18 to 2.53); *P* = .005	2.05 (1.23 to 3.41); *P* = .006	1.58 (0.89 to 2.83); *P* = .12	2.18 (1.13 to 4.22); *P* = .02	2.09 (0.88 to 4.96); *P* = .10
B-cell neoplasms other than CLL/SLL or plasma cell disorders (n = 264)					
β (95% CI), male vs female	0.40 (0.15 to 0.64)	0.37 (0.07 to 0.68)	0.05 (−0.32 to 0.43)	0.41 (0.00 to 0.81)	0.11 (−0.42 to 0.64)
% reduction (95% CI); *P* value, in β vs model 1 or 1A**			86.5 (−6.9 to 179.8); *P* = .07	<0; *P* = .87	70.4 (−71.3 to 212.2); *P* = .33
% reduction (95% CI); *P* value, in β vs model 3**					72.9 (−57.0 to 202.8); *P* = .27
HR (95% CI); *P* value, male vs female††	1.49 (1.17 to 1.90); *P* = .001	1.45 (1.07 to 1.97); *P* = .016	1.06 (0.73 to 1.53); *P* = .78	1.50 (1.00 to 2.25); *P* = .05	1.12 (0.66 to 1.89); *P* = .68

* CI = confidence interval; CLL/SLL = chronic lymphocytic leukemia/small lymphocytic leukemia; HR = hazard ratio; NA: percent change in β from model 1, 1A, or 3 not calculated when β in model 1, 1A, or 3 was small (0–0.08).

† White, black, Hispanic, Asian/Pacific Islander, other race.

‡ All models 1A restricted to participants with complete data on all covariables in multivariable regression models (n = 45 726 in cohort; n = 2332 cases).

§ All models 2 and 4 were adjusted for height and height-squared.

‖ All models 3 and 4 were adjusted for age, race, education (≤high school graduate, some college, ≥college graduate), marital status (never married, married/cohabitating, separated/divorced, widowed), body mass index (<25, 25–25.9, ≥30 kg/m^2), physical activity (none and tertiles of MET-hours/week), pack-years of smoking (continuous), pack-years squared (continuous), years smoked (continuous), alcohol at age 45 (none, <1, 1–2, ≥2 drinks/day), fruit and vegetable consumption (without potatoes; continuous), red meat consumption (continuous), energy intake (continuous), 10-year use of low-dose aspirin, regular-strength aspirin, or nonaspirin nonsteroidal anti-inflammatory drugs (as separate terms; nonuser, low use [<4 days/week or <4 years], high use [≥4 days/week for ≥4 years]), and self-rated health (excellent, very good, good, fair, poor). Alcohol intake at age 45 was included because it was a better predictor of total cancer incidence in this cohort than alcohol intake at baseline. Smoking was adjusted for by inclusion of three variables—pack-years, pack-years squared, and years smoked—because these three variables all contributed statistically significantly to lung cancer risk in this cohort. Models 3 and 4 are based on participants with complete data on all covariables (n = 45 726 in cohort; n = 2332 cases).

¶ Includes cancers of the gastrointestinal tract, lung, urinary system, head and neck, connective tissue, brain, and endocrine system, as well as melanoma and hematologic malignancies. Models 3 and 4 for shared-site cancers additionally adjusted for family history of colon cancer, lung cancer, hematologic malignancies, pancreatic cancer, melanoma, or bladder cancer (as separate terms; yes/no); sigmoidoscopy in the past 10 years (yes/no), years of estrogen therapy (never, 1–4, 4.1–9, >9), years of combined hormone therapy (never, 1–4, 4.1–9, >9), 10-year use of acetaminophen (nonuser, low use [<4 days/week or <4 years], high use [≥4 days/week for ≥4 years]), diabetes (yes/no), pancreatitis (yes/no), high blood pressure medication use (yes/no), kidney disease (yes/no), chronic obstructive pulmonary disease (yes/no), fatigue (yes/no), rheumatoid arthritis (yes/no), freckles at 10–20 years (yes/no), three or more sunburns at 10–20 years (yes/no), red/blond hair at 10–20 years (yes/no), reaction to 1 hour in strong sunlight (severe sunburn/blisters, painful sunburn/peeling, mild burn/tan, tan/no sunburn, don't know), personal history of nonmelanoma skin cancer (yes/no), and history of mole biopsy (yes/no).

\# Major categories do not add up to 3466 cases because of exclusion of cancer sites with less than 100 cases.

** Percent reduction in β is based on model 2 vs model 1, model 3 vs model 1A, model 4 vs model 1A, and model 4 vs model 3. Note that this "proportion" is not bounded by 0 and 1. A less than 0% reduction in β means that after adjustment for explanatory factors, the sex difference became greater than before adjustment. A greater than 100% reduction in β means that after adjustment for mediators, women are at greater risk than men. Two-sided P-values are provided for the hypothesis that the βs for sex in the models with and without height were equal (see Methods section for details).

†† Two-sided *P* values are provided for the association between male sex and cancer risk.

‡‡ Besides cancers of colon/rectum and pancreas, contains cancers of esophagus, stomach, liver, small intestines, anus and anal canal, gall bladder, biliary tract, and other or ill-defined digestive organs. Models 3 and 4 for cancers of the gastrointestinal tract additionally adjusted for family history of colon cancer or pancreatic cancer (as separate terms; yes/no); sigmoidoscopy in the past 10 years (yes/no), years of estrogen therapy (never, 1–4, 4.1–9, >9), years of combined hormone therapy (never, 1–4, 4.1–9, >9), diabetes (yes/no), and pancreatitis (yes/no).

§§ Models 3 and 4 for lung cancer additionally adjusted for family history of lung cancer (yes/no) and chronic obstructive pulmonary disease (yes/no).

|||| Besides cancers of kidney and bladder, contains cancers of renal pelvis, ureter, and other/unspecified urinary organs. Models 3 and 4 for urinary cancers additionally adjusted for family history of bladder cancer (yes/no), high blood pressure medication use (yes/no), and kidney disease (yes/no).

¶¶ Models 3 and 4 for melanoma additionally adjusted for family history of melanoma (yes/no), freckles at 10–20 years (yes/no), three or more sunburns at 10–20 years (yes/no), red/blond hair at 10–20 years (yes/no), reaction to 1 hour in strong sunlight (severe sunburn/blisters, painful sunburn/peeling, mild burn/tan, tan/no sunburn, don't know), personal history of nonmelanoma skin cancer (yes/no), and history of mole biopsy (yes/no).

\## Models 3 and 4 for thyroid cancer additionally adjusted for years of estrogen therapy (never, 1–4, 4.1–9, >9) and years of combined hormone therapy (never, 1–4, 4.1–9, >9).

*** Models 3 and 4 for hematologic malignancies additionally adjusted for: family history of hematologic malignancies (yes/no), 10-year use of acetaminophen (nonuser, low use [<4 days/week or <4 years], high use [≥4 days/week for ≥4 years]), fatigue (yes/no), and rheumatoid arthritis (yes/no).

the mediating factor(s). In our analyses, the percent reduction in β corresponds to the proportion of the overall sex difference in cancer risk explained by height when comparing model 2 with model 1, whereas it corresponds to the proportion explained by height of the sex difference that remains after controlling for other factors when comparing model 4 with model 3. As shown in Table 4, β was reduced by 33.8% (95% CI = 10.2% to 57.3%) when the age- and race-adjusted model was additionally adjusted for height and height squared (HR = 1.34; 95% CI = 1.21 to 1.48) and by 47.0% (95% CI = –4.1% to 98.0%) when a multivariable-adjusted model was additionally adjusted for height and height squared (HR = 1.19; 95% CI = 1.01 to 1.41). In other words, the associations with male sex became less pronounced after adjustment for height measures. Four individual cancer sites also showed statistically significant reductions in β between models 2 and 1: 42.0% reduction for urinary cancers, 90.9% for kidney cancer, 57.3% for melanoma, and 49.6% for hematologic malignancies. For kidney cancer and melanoma, the sex difference was no longer statistically significant. Similar observations were made for these four cancer sites when comparing the multivariable models 4 and 3, with magnitudes of percent reduction in β ranging from 36.2% for hematologic malignancies to greater than 100% for kidney cancer (ie, reversal from increased male risk to increased female risk); however all but melanoma were no longer statistically significant. For comparison, the multiple other risk factors only accounted for a non-statistically significant 23.1% of the sex difference in cancer risk at shared sites, with a wide range across sites (model 3 vs 1A).

Discussion

Although numerous explanations for the excess risk of cancer for men vs women at most shared anatomic sites have been proposed (2–7), height and body size have rarely been mentioned as explanatory factors, and no study has hitherto attempted to quantify this pathway. We therefore used the technique of mediation analysis to ask a fundamental question—namely, to what degree the height difference between men and women accounts for the fact that men are at higher risk for many shared cancers. The importance of such analyses (ie, analyses to understand the totality of processes that explain an observed relationship between risk factor/exposure and disease) has been increasingly recognized in epidemiologic research (29).

As proposed by Baron and Kenny, mediation requires that the exposure be associated with the mediator and that the mediator be associated with the outcome independent of exposure (27). The first criteria, an association between sex and height, is well established, whereas the second was demonstrated in this study for cancer of shared sites overall and for several cancer site groupings, generally consistent with prior studies (8–22); an additional criterion, that the exposure be associated with the outcome when the mediator is not in the model, is no longer considered required on theoretical or statistical grounds (30). In this study, for all shared cancer sites, men had a 55% increased risk of cancer. When height and height squared were included in the model as measures of body size, 33.8% of the excess risk for men was explained by the height differences between men and women. Height was also a statistically significant mediator for four site groupings (urinary system cancer overall and kidney cancer in particular, melanoma, and hematologic cancers), with the proportion mediated by height ranging from 42.0% to 90.9%. For the other sites, including gastrointestinal, lung, and bladder cancer, height did not meet the criteria of being a mediator of the sex–cancer association.

In our analyses, we also considered multiple factors other than height that may explain the sex difference in cancer incidence at various sites; these factors may represent other explanatory pathways (ie, mediators) between male sex and increased cancer risk. In the analysis of risk of cancer at shared sites, adjustment for more than 35 demographic, lifestyle, and medical cancer risk factors, including detailed adjustment for smoking, accounted for only 23.1% of the sex difference in cancer incidence overall but varied widely across cancer sites. Finally, by controlling for these factors, we estimated the proportion of the remaining sex difference that was explained by height: 47.0% for all shared sites combined. For the four sites for which there was evidence of mediation by height, the percent mediated by height was similar to that in the models without the other mediators but generally no longer statistically significant. Thus, these data indicate that height or body size constitutes an important explanatory factor for the observed increase in cancer risk for men overall and for some specific sites. Notably, height accounted for about half or more of the sex difference in melanoma, kidney cancers, and hematopoietic malignancies but essentially none of the difference in cancers that are strongly related to tobacco use, namely lung and bladder.

The observations that some cancers (eg, thyroid or breast) are less rather than more common among men and height is associated with some cancers but not others indicate there are multiple biologic and behavioral mechanisms that vary by anatomic site that may explain the sex differences in cancer risk. One postulated mechanism related to height is that taller individuals may be at increased risk of cancer because of a larger number of cells and higher rate of cell divisions within tissues (31). Consistent with this hypothesis, for instance, a case–control study reported a strong association between melanoma risk and body surface area, as measure of skin cell mass at risk of malignant transformation (32). Proposed mechanisms contributing to the association between height and cancer risk, perhaps by influencing the number of proliferating cells and/or other pathways, include genetic factors, energy intake in early life, and exposure to sex and growth hormones. Of particular interest are insulin-like growth factors (IGFs), well known pivotal regulators of energy metabolism and growth. For example, IGF-1 is considered a major regulator of childhood growth (33), and childhood IGF-1 levels are strongly linked to subsequent growth in both leg and trunk length (34). Adult height is associated with circulating IGF-1 levels in some but not all studies (35–38), suggesting that it is early exposure that influences both height and risk of cancers in adulthood. Indeed, increasing evidence suggests that IGF-1 levels may influence the risk of development of a variety of human cancers (39,40). This notion is supported by several prospective studies that have indicated a relationship between circulating IGF-1 levels and the risk of prostate, breast, colorectal, and other cancers (39). Clearly, given the many factors that influence height, this variable is likely a surrogate biomarker for a variety of genetic or environmental factors that may be amenable for mediation analyses in the future.

This study has several strengths, including its prospective design, size, and case ascertainment through the SEER cancer

registry. Furthermore, the availability of baseline information on anthropometrics, personal lifestyle, and medical history allowed adjustment for numerous known or potential cancer risk factors that may also explain the sex difference in cancer risk.

There are limitations that need to be acknowledged. First, the measurement error in self-reported height would include both a random component and a systematic component that might be influenced by sex. For example, in the 2001 to 2006 National Health and Nutrition Examination Survey, height is overreported by an average of 0.48 inches (1.2 cm) and 0.27 inches (0.7 cm) by men and women, respectively (41). Other studies had similar conclusions (42–44). This small difference between men and women in overreporting of height would likely lead to a spuriously greater reduction in the β for sex when height was in the model and an overestimation of the percentage of the sex difference explained by height, whereas the random component of error in height would bias the results in the opposite directions, so the combined effects cannot be predicted.

Similarly, data on the demographic, lifestyle, and medical history variables that were considered potential explanatory factors for the sex difference other than height were subject to measurement error and could bias our results. In addition, we did not have information on one category of other major explanatory factors for the male excess of cancer—namely, occupational exposures that are related to cancer risk; these would have been appropriate to adjust for in models 3 and 4. For example, at-risk populations include workers exposed to asbestos, arsenic, chloromethyl ethers, and polycyclic aromatic hydrocarbons for the development of lung cancer (2) and workers exposed to dyestuff, aromatic amines, rubber, leather, and aluminum for the development of bladder cancer (7). Because male sex, and possibly height, is related to occupation, our inability to include information on occupational factors would have spuriously reduced the percent of the sex–cancer association explained by other factors and could have biased our results of the proportion of the remaining sex–cancer association that was mediated by height in either direction. We also had small numbers of cases for some cancer sites, limiting our power for those analyses, and because we chose to examine multiple cancer outcomes, there is the possibility of false-positive results. Finally, our study participants were primarily middle-class Americans, and therefore our results might not pertain to populations in which early malnutrition impacts maximal height.

Methods for mediation analyses are an area under development in epidemiology and other fields (30,45–48). In this study, mediation was evaluated by the difference in β coefficients for sex between models with and without the mediators. For simple models, the difference of coefficients approach is equivalent to the product of coefficients method developed in the social sciences for continuous outcomes (46), and the two methods are also approximately equivalent in Cox models with a rare outcome (47). Our approach accounted for other mediators (as discussed above) but did not include the complex effects of possible interactions between exposure and mediators (45,48).

In conclusion, this study is the first to investigate and quantify the degree to which height is an explanatory factor for the increased risk of men for many shared-site cancers. Our findings provide evidence that some portion of the excess risk of various cancer types among men is due to factors associated with height (eg, number of susceptible cells in a specific organ or growth-influencing exposures in childhood).

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