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Research Article

Adult Stature and Risk of Cancer at Different Anatomic Sites in a Cohort of Postmenopausal Women

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Abstract

Background: Prospective studies in Western and Asian populations suggest that height is a risk factor for various cancers. However, few studies have explored potential confounding or effect modification of the association by other factors.

Methods: We examined the association between height measured at enrollment in 144,701 women participating in the Women's Health Initiative and risk of all cancers combined and cancer at 19 specific sites. Over a median follow-up of 12.0 years, 20,928 incident cancers were identified. We used Cox proportional hazards models to estimate HR and 95% confidence intervals (CI) per 10 cm increase in height, with adjustment for established risk factors. We also examined potential effect modification of the association with all cancer and specific cancers.

Results: Height was significantly positively associated with risk of all cancers (HR = 1.13; 95% CI, 1.11–1.16), as well as with cancers of the thyroid, rectum, kidney, endometrium, colorectum, colon, ovary, and breast, and with multiple myeloma and melanoma (range of HRs: 1.13 for breast cancer to 1.29 for multiple myeloma and thyroid cancer). These associations were generally insensitive to adjustment for confounders, and there was little evidence of effect modification.

Conclusions: This study confirms the positive association of height with risk of all cancers and a substantial number of cancer sites.

Impact: Identification of single-nucleotide polymorphisms associated both with height and with increased cancer risk may help elucidate the association. *Cancer Epidemiol Biomarkers Prev; 22(8); 1353–63. ©2013 AACR.*

Introduction

A number of large prospective studies in Western and Asian populations (1–6) have indicated that height may be an independent risk factor for various cancers. In a recent meta-analysis (4), height was modestly associated with risk of all cancers combined [summary relative risk per 10 cm increase: 1.10 (95% confidence interval (CI), 1.08–1.12) in men and 1.15 (95% CI, 1.14–1.17) in women]. The largest study to date, the Million Women Study (4), reported significant associations for 10 of 17 specific cancer sites/types ranging from HRs of 1.14 (95% CI, 1.05–1.24) for rectum to 1.32 (95% CI, 1.22–1.42) for melanoma. The largest studies of cancer incidence have showed some consistency about the specific cancer sites/types for which height is a risk factor (refs. 2, 4, and 5; melanoma, thyroid, ovary, colorectum, breast), but there are inconsistencies as well (lung, brain). Furthermore, the magnitude of the associations for specific cancer sites has varied among studies.

Adult height is influenced by both genetics and early life exposures (7). Some common biological mechanisms may underlie the associations of height with different cancer sites/types, but, given differences in the magnitude of the association by site/type, it is also possible that some mechanisms differ by site. However, at the outset, it is important to identify those sites/types which show an independent association with height after adjustment for appropriate covariates. Few studies have examined potential confounding of the association of height with specific cancer sites/types in depth. A number of studies used the same (study-specific) multivariable model for different cancer sites (1, 2, 4). One issue, in particular, given the correlation between height and weight, is what

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is the appropriate way to adjust for body weight to assess the independent association of height with cancer risk? (8). In addition, few studies (4, 5) have assessed possible effect modification of the association of height with specific cancer sites.

We used data from the Women's Health Initiative (WHI) to examine the association of height, measured at baseline as well as during follow-up, with risk of incident cancer among postmenopausal women and to determine to what extent the observed association was affected by confounding and effect modification.

Materials and Methods

Study population

The WHI is a large, multicenter, multifaceted study designed to advance understanding of the determinants of major chronic diseases in postmenopausal women. It is composed of a clinical trial component ($N = 68,132$) and an observational study component ($N = 93,676$; ref. 9). The clinical trial component included 3 randomized controlled interventions: hormone therapy, low-fat diet modification, and calcium–vitamin D supplementation. Women between the ages of 50 and 79 years and representing major racial/ethnic groups were recruited from the general population at 40 clinical centers throughout the United States between 1993 and 1998. Details of the design and reliability of the baseline measures have been published (9, 10).

Data collection and variable definition

At study entry, self-administered questionnaires were used to collect information on demographics, medical, reproductive, and family history, and on dietary and lifestyle factors, including smoking history, alcohol consumption, and recreational physical activity. All participants had their weight, height, and waist and hip circumferences measured by trained staff at baseline. Weight was measured to the nearest 0.1 kg, and height to the nearest 0.1 cm. Anthropometric measurements were also made during follow-up (in years 3 and 6 for the majority of the cohort; in years 1 and 9 for a minority of women). Body mass index (BMI) was computed as weight in kilograms divided by the square of height in meters. Questions about physical activity at baseline referred to a woman's usual pattern of activity, including walking and recreational physical activity. A variable "current total leisure-time physical activity" (MET-hours/week) was computed by multiplying the number of hours per week of leisure-time physical activity by the metabolic equivalent (MET) value of the activity and summing the products of all types of activities (11).

Clinical outcomes (including new cancer diagnoses) were updated semiannually in the clinical trial and annually in the observational study using in-person, mailed, or telephone questionnaires. Self-reports of malignancy were verified by centralized review of medical records and pathology reports by trained physician adjudicators (12). As of April 2, 2012, a total of 24,309 incident cancers had been diagnosed among the 161,808 participants in the observational study and clinical trial after a median of 12.0 years of follow-up. The proportion of the cohort that was lost to follow-up was less than 1%.

For the analyses reported here, we excluded women with a previous history of cancer, except nonmelanoma skin cancer ($N = 16,256$) and those missing information on height ($N = 851$), leaving 144,701 women available for analysis among whom 20,928 had one or more invasive cancer diagnoses during follow-up. In the analysis of individual cancer sites/types, if a woman had more than one cancer diagnosis, we selected the earliest. For the analysis focusing on endometrial cancer, women who reported a history of hysterectomy at baseline ($N = 1,113$) were excluded; similarly women with a history of bilateral oophorectomy ($N = 686$) were excluded from the analysis focused on ovarian cancer.

Statistical analysis

Given that some cancers are associated with BMI and that both weight and BMI are associated with height, it is necessary to adjust for weight/BMI to estimate the independent association of height with cancer at specific sites (8). However, it is unclear how best to conduct this adjustment. We previously examined the scaling of weight-for-height in relation to risk of cancer at specific sites (13) to determine the scaling that was mostly strongly associated with weight and least associated with height. For each site, we examined weight/height^X (W/H^X), where X ranged from 0 to 3.0 in increments of 0.1 and selected the value of W/H^X that was most strongly associated with weight and least strongly associated with height. We used this site-specific scaling to adjust for body weight. In this study, we used this approach in the WHI population and compared it to the more common approach of including BMI in the multivariable model. For each cancer site, we present the results of age-adjusted (HR1) and several multivariable-adjusted models (HR2—covariates not including BMI; HR3—covariates + BMI; and HR4—covariates + weight/height^X—that is, the scaling of height that was most strongly associated with weight and least associated with height (13).

Cox proportional hazards models, with time-to-event in days as the time scale, were used to estimate HR and 95% CIs for the association of height with cancer risk. We examined the association of height categorized by quintiles with risk of all cancers and we also computed the HR for all sites combined and for each individual site per 10 cm increase in height. The following covariates were included in the main multivariable model: age at enrollment (continuous); years of education (less than high school graduate, high school graduate/some college, college graduate, post-college); pack-years of smoking (continuous); alcohol consumption (drinks per week—continuous); and hormone therapy (ever, never). An alternative model included type of hormone therapy (never, estrogen only, estrogen + progestin, both estrogen only and estrogen + progestin) for the analysis of breast and colorectal

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cancer. Other covariates were added to the models for specific cancer sites to reflect established risk factors (see footnotes to Table 3). Because cancer screening was positively correlated with height and because some cancers may be detected due to screening, in additional models we adjusted for the effects of screening on all cancers, and cancers of the breast, colorectum, and cervix. HRs and 95% CIs for 19 different site/types per 10 cm increase in height are presented in decreasing order of magnitude in a forest plot in which each cancer site is represented by a square and a horizontal line, which denote the point estimate and the 95% CI, respectively. In those forest plots, the size of the square represents the weight of the outcome, the solid vertical line indicates the null value (1.0), and the broken vertical line and diamond indicate the summary estimate.

In addition to analyses using height at baseline, we analyzed the repeated height measurements as time-dependent covariates in relation to risk of any cancer and sites with the largest number of cases [breast, colorectum, melanoma, lung (in ever smokers), and endometrial cancer] in Cox proportional hazards models to account for fluctuations in the measurements over time (14). With this approach, the predictive significance of various aspects of these measures was evaluated, including the average of all measurements and time-lagged values (1–3 years, 2–4 years, and 3–5 years prior to diagnosis of cancer). The relevant time-dependent covariate for participants at risk at time t was a function of measurements obtained only until the time of diagnosis in the case.

Forest plots were also used to present the results of stratified analyses to assess whether the association of height with cancer risk varied by level of potential effect modifiers, including education level, weight, waist circumference, smoking status (never, <20 pack-years, ≥20 pack-years), age at menarche, parity, menopausal status, oral contraceptive use, hormone therapy, and self-reported health status (excellent/very good/good or fair/poor). These analyses were carried out for all cancers combined and for cancers of the breast, colorectum, melanoma, lung cancer in ever smokers, and endometrial cancer (sites with the largest number of cases). We formally tested for interactions between height (<162 cm/≥162 cm) and potential effect modifiers by comparing the fit of models with and without the product terms representing the variables of interest using a likelihood ratio test. All statistical significance tests were two-sided. All analyses were conducted using SAS version 9.2 (SAS Institute Inc.).

Results

Mean age and BMI decreased across increasing quintiles of height, whereas mean weight, MET-hours/week, pack-years of smoking, and alcohol intake increased with increasing height (Table 1). The proportions of participants with post-college education, with an income of $75,000 or greater, and of ever users of oral contraceptives, ever users of hormone therapy, current smokers, and Blacks and Whites increased with increasing height, whereas the proportion of participants of Hispanic ethnicity and with an early age at menarche decreased with increasing height. Rates of mammography and Pap screening were high among WHI participants at baseline and increased modestly over quintiles of height, whereas there was no trend in the frequency of colorectal cancer screening. The proportions of nulliparous women and women with a late age at first birth varied little over the range of height.

Height was significantly and positively associated with risk of all cancers combined in all models adjusting for various factors (Table 2). In the age-adjusted model, the HR per 10 cm increase in height with all cancer was 1.15 (95% CI, 1.12–1.17). After adjustment for all important potential confounders (age, hormone therapy, pack-years of smoking, alcohol intake, age at menarche, weight/height^X, education, ethnicity, and study allocation in the clinical trials), the HR was 1.13 (95% CI, 1.11–1.16). Similar patterns were seen in women of different age groups (50–59, 60–69, and 70–79 years) and different income levels (<$20,000; $20,000–<50,000; $50,000–<100,000; ≥$100,000; data not shown).

In age-adjusted models (HR1), height was significantly positively associated with 7 cancer sites/types (HR1: colorectum, colon, breast, endometrium, thyroid, melanoma, and multiple myeloma; Table 3). Several other cancers showed borderline associations [rectum, kidney, brain, ovary, non-Hodgkin's lymphoma (NHL), and multiple myeloma]. After adjustment for covariates not including body weight (HR2), height was significantly associated with 9 sites/types (colorectum, colon, rectum, breast, ovary, kidney, thyroid, melanoma, and multiple myeloma). When BMI was included in the multivariable model (HR3), 9 sites/types showed statistically significant associations with height (colorectum, colon, rectum, breast, endometrium, kidney, thyroid, melanoma, and multiple myeloma). When site-specific scaling of W/H^X was used (HR4), the same 9 sites plus ovarian cancer showed significant associations with height. In addition, cancers of the brain, lung (in ever smokers), and NHL showed borderline associations.

Figure 1 shows the ranking (in descending order of magnitude) of the associations of height with risk of cancer at specific anatomic sites using HR4 (site-specific scaling of W/H^X). Of 19 cancer sites, none showed an inverse association with height.

We considered the possibility that cancer screening might be a confounder of the association of height with cancer. Inclusion of mammography or Pap screening in the model for all cancers (as an indicator of preventive screening in general) did not affect the association with height (Table 2). Inclusion of mammography screening in the model for breast cancer and inclusion of colorectal cancer screening in the model for colorectal cancer (with follow-up starting 1 year post-baseline to accord with the screening information obtained 1 year post baseline) did not alter the associations with height. When Pap screening

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Table 1. Baseline characteristics by quintiles of height in the WHI

	Quintiles of height in cm				
	<156.5	156.5–<160.2	160.2–<163.5	163.5–<167.1	≥167.1
N	28,536	29,291	29,180	28,912	28,782
Mean person-years	295,762	312,015	315,329	314,447	315,208
Mean age (y)	65.1	63.8	63.0	62.3	61.1
Mean weight (kg)	66.8	70.9	73.5	75.7	79.8
Mean BMI (kg/m^2)	28.5	28.2	28.1	27.7	27.4
Mean MET-h/wk[a]	11.4	11.8	11.9	12.0	12.2
Mean pack-years of smoking	8.2	9.2	9.8	9.9	10.5
Mean servings of alcohol/wk	1.7	2.1	2.4	2.6	2.9
Education, % >16 y	23.1	26.4	27.7	30.4	34.9
Ethnicity					
White, %	72.5	81.7	84.6	86.1	87.3
Black, %	7.4	9.0	9.3	9.7	10.3
Hispanic, %	9.4	4.9	3.2	2.1	1.0
Other, %	10.7	4.4	2.9	2.1	1.4
Income ≥$75,000	13.2	16.7	17.9	20.1	23.0
Parity, % nulliparous	10.9	10.6	11.0	11.2	14.4
Age of menarche,% <12 y	27.1	23.4	21.9	20.1	16.9
Age at first birth,% ≥30 y[b]	10.0	8.5	8.2	8.7	9.8
Oral contraceptive use, % ever	33.8	39.1	42.3	45.3	49.3
Hormone therapy, % ever	52.4	54.7	57.5	58.1	60.3
Current smokers, %	6.0	6.7	7.1	7.1	7.8
Mammography screening[c]	81.9	82.7	83.3	84.0	84.5
Pap screening[d]	86.3	88.4	88.6	89.5	90.0
Colorectal cancer screening[e]	43.2	43.7	44.5	44.4	44.2

[a]Defined as caloric need per kilogram of body weight per hour of activity divided by the caloric need per kilogram of body weight per hour of rest, per hour per week.
[b]*N* parous women = 117,603.
[c]Had mammogram within past 2 years.
[d]Had Pap screening within past 3 years.
[e]Had any screening in the year before year 1 visit: rectal exam, Hemoccult, or colonoscopy or sigmoidoscopy.

was included in the model for cervical cancer, the HR was reduced to 1.21 (95% CI, 0.80–1.86) from 1.38 (95% CI, 0.96–1.99; data not shown).

We repeated the analysis on the total cohort of 161,808 women, including the 16,256 who had a history of previous cancer. The association of height with any cancer and with specific cancer sites was not materially different in the total cohort.

In analyses treating height as a time-dependent covariate, the results for all cancers combined and for cancers of the breast, colorectum, lung (in ever smokers), and melanoma were similar to those using only baseline height (data not shown).

As anticipated, younger women and women with higher income had greater mean height compared to older women and women with lower income, respectively (mean height for women <63 years old vs. women ≥63 years old: 163 and 161 cm, respectively; mean height for women with income <$50,000 vs. ≥$50,000: 161 and 163 cm, respectively). Nevertheless, the association of height with all cancers (Fig. 2) and cancers of the breast, colorectum, lung (in ever smokers), endometrium, as well as melanoma, did not vary by age or income, or, with few exceptions, by other characteristics (Supplementary Figs. S1–S5). Statistically significant differences in the HRs for height were limited to weight and health status for breast cancer (Supplementary Fig. S1) and age at enrollment for melanoma (Supplementary Fig. S3). For colorectal cancer, lung cancer in ever smokers, and endometrial cancer (Supplementary Figs. S2, S4, and S5, respectively), risk did not differ by levels of any factor.

Discussion

In this analysis of postmenopausal women aged 50 to 79 years at baseline, height was positively associated with risk of all cancers combined and of cancer at a number of specific anatomic sites. The sites showing statistically significant associations were multiple myeloma, thyroid,

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Table 2. Effect of adjustment for different potential confounding variables on the association of height with all cancer (per 10 cm increment) in the WHI

	HR	95% CI
Adjusted for age only	1.15	1.12–1.17
Additionally adjusted individually for		
Education years	1.14	1.12–1.17
Ethnicity	1.13	1.11–1.16
Smoking (pack-yrs)	1.13	1.11–1.16
Weight (kg)	1.12	1.09–1.14
BMI (kg/m^2)	1.17	1.14–1.19
Alcohol intake (servings)	1.14	1.12–1.17
Physical activity (MET-hrs/wk)	1.15	1.12–1.17
Age at menarche	1.16	1.13–1.18
Oral contraceptive use (ever)	1.15	1.12–1.17
Hormone therapy (ever)	1.15	1.12–1.17
Hormone therapy (type)[a]	1.15	1.12–1.17
Parity	1.15	1.12–1.17
Age at menopause	1.15	1.12–1.17
Mammography in past 2 years	1.15	1.13–1.18
Pap screening in past 3 years	1.15	1.12–1.19
Adjusted for main covariates[b]	1.13	1.11–1.16

[a]Never, estrogen alone, estrogen + progestin, both E and E + P.

[b]Age (continuous), hormone therapy (yes, no), pack-years of smoking (continuous), alcohol intake (continuous), W/H$^{1.7}$ (continuous), age at menarche (<12, 12, 13, >13), education (less than high school grad, high school grad/some college, college grad, post-college), ethnicity (White, Black, other), randomization to treatment arm of clinical trials (yes, control, placebo, not randomized).

rectum, kidney, colorectum, colon, endometrium, ovary, melanoma, and breast. NHL and cancers of the brain and of the lung in ever smokers showed borderline significant associations. The observed associations were not explained by other known risk factors, including cancer screening. Furthermore, the association of height with all cancers and with cancers of the breast, colorectum, lung, and endometrium, as well as melanoma, varied little when stratified by a large number of potential effect modifiers. Of 19 cancer sites, none showed a significant inverse association with height. When the average of all height measurements was used, the association with any cancer, cancers of the breast, colorectum, endometrium, and lung cancer in ever smokers, and of melanoma remained unchanged.

To minimize possible confounding due to the correlation of both weight and BMI with height (Pearson correlation coefficient: 0.26, $P < 0.0001$ and -0.08, $P < 0.0001$, respectively), we used site-specific scaling of W/H^X. Although in general the results were similar to those obtained using BMI, the magnitude of associations was affected in some cases (the largest change was the reduction in the HR for rectal cancer from 1.37 to 1.25), and that for ovarian cancer was statistically significant when adjusting for the site-specific scaling by but not BMI.

Results of this study are consistent with those of 2 previous cohort studies conducted in women in the West (4, 5). All 3 studies reported significant associations with melanoma and cancers of the colorectum, kidney, endometrium, breast, and ovary. Two of the 3 additionally reported significant associations with leukemia (4, 5) and thyroid cancer (5, this study). For multiple myeloma, brain cancer, and NHL, the association with height was significant in either the Million Women Study (4) or this study and each verged on statistical significance in the other. A cohort study from Korea (2) observed significant associations between height and cancers of the thyroid, ovary, breast, colon, and leukemia in women (1, 3, 6). Less consistent associations were seen for cancers of the bladder and lung (1–6).

Review of the largest cohort studies as well as pooled analyses of some individual cancers (2–5, 15–25) suggests that the associations of height with risk of melanoma and with cancers of the thyroid, ovary, colorectum, breast, endometrium, and kidney are unlikely to be due to confounding. Concerning effect modification, in this study the association of height with risk of any cancer varied little by level of other variables. Two previous studies (4, 5) reported that the association of height with any cancer was stronger among never smokers; however, in this study the association did not differ by smoking level (never, <20, ≥20 pack-years). (There were too few current smokers to compute a stable estimate for current smokers.) Our analysis of effect modification for those sites/types with the largest numbers (breast, colorectum, melanoma, lung cancer in ever smokers, and endometrium) also showed limited evidence of effect modification. This latter finding is in agreement with that of Green and colleagues (4), who found no evidence of effect modification for cancers of the breast, lung, colon, endometrium, and ovary in the Million Women Study. However, our statistical power to assess effect modification was limited.

Adult height is determined both by genetics and by early life exposures (7, 26), and environmental circumstances influence the attainment of one's genetic potential (7, 26). The influence of environmental exposures on height is evidenced by the secular increase in the height of populations in many countries beginning in the 19th century, probably reflecting improvements in hygiene and nutrition (26). Height should thus be thought of as a marker for one or more exposures that influence cancer risk rather than a risk factor itself. Of particular relevance are findings that adult height is associated with a higher energy intake in childhood and adolescence (27), higher intake of milk protein in premenarchic girls (28), and higher circulating levels of insulin-like growth factor (IGF-I; ref. 29). Milk intake in childhood and adulthood is positively associated with increased levels of circulating IGF-I, and in children higher circulating IGF-I promotes

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Table 3. HRs and 95% CIs for the association of height (per 10 cm increase) with specific cancers in the WHI

Cancer site	*N* cases	HR1	95% CI	HR2	95% CI	HR3	95% CI	HR4	95% CI
Colorectum[a]	1,904	1.13	1.05–1.21	1.15	1.07–1.24	1.19	1.10–1.28	1.17	1.09–1.26
Colon[b]	1,516	1.13	1.04–1.22	1.14	1.04–1.24	1.18	1.08–1.29	1.16	1.07–1.26
Rectum[b]	257	1.22	1.00–1.48	1.26	1.03–1.55	1.37	1.10–1.70	1.25	1.02–1.53
Breast[c]	6,798	1.14	1.10–1.18	1.11	1.07–1.16	1.14	1.09–1.18	1.13	1.08–1.17
Endometrium[d]	1,109	1.18	1.07–1.29	1.10	1.00–1.22	1.19	1.08–1.31	1.16	1.07–1.26
Ovary[e]	683	1.11	0.99–1.25	1.14	1.01–1.29	1.11	0.98–1.26	1.13	1.00–1.29[f]
Cervix[g]	83	1.30	0.93–1.83	1.41	0.99–2.01	1.42	0.99–2.02	1.38	0.96–1.99
Kidney[h]	369	1.18	1.00–1.38	1.23	1.03–1.45	1.26	1.06–1.50	1.23	1.05–1.43
Bladder[g]	457	1.13	0.97–1.30	1.05	0.90–1.22	1.05	0.90–1.22	1.06	0.90–1.24
Thyroid[i]	270	1.27	1.06–1.54	1.32	1.08–1.62	1.33	1.08–1.63	1.29	1.05–1.58
Lung (NS)[j]	269	1.12	0.93–1.36	1.13	0.93–1.37	1.20	0.98–1.47	1.12	0.92–1.38
Lung (ES)[g]	1,466	0.99	0.91–1.07	1.00	0.92–1.09	0.98	0.90–1.07	1.09	1.00–1.19
Stomach[g]	152	0.98	0.77–1.26	1.01	0.78–1.31	1.02	0.79–1.33	1.05	0.82–1.35
Pancreas[g]	459	1.03	0.90–1.19	1.03	0.89–1.20	1.03	0.89–1.21	1.03	0.89–1.20
Melanoma[g]	1,169	1.29	1.17–1.41	1.15	1.04–1.26	1.16	1.05–1.27	1.15	1.04–1.26
Brain[g]	176	1.26	1.00–1.59	1.28	1.00–1.63	1.28	1.00–1.65	1.26	0.99–1.62
Leukemia[g]	447	1.09	0.94–1.26	1.04	0.89–1.21	1.04	0.89–1.22	1.05	0.90–1.22
NHL[g]	888	1.11	1.00–1.23	1.11	1.00–1.24	1.11	1.00–1.24	1.11	0.99–1.23
Multiple myeloma[g]	282	1.29	1.07–1.56	1.30	1.07–1.57	1.28	1.06–1.56	1.29	1.06–1.57
All cancers[h]	20,928	1.15	1.12–1.17	1.12	1.10–1.15	1.14	1.11–1.16	1.13	1.11–1.16

NOTE: Shading indicates statistically significant associations. Women with a history of bilateral oophorectomy were excluded from the analysis of ovarian cancer, and women with a history of hysterectomy were excluded from the analysis of endometrial cancer.

Abbreviations: HR1, age-adjusted; HR2, multivariable-adjusted but without weight or BMI; HR3, multivariable-adjusted + BMI; HR4, multivariable + site-specific scaling of W/H^X; NS, never smoker; ES, ever smoker.

[a]HR2 adjusted for age (continuous), servings of alcohol per week (continuous), pack-years of smoking (continuous), hormone therapy (ever, never), age at menarche (<12, 12, 13, >13), family history of colorectal cancer (yes, no, missing), physical activity (MET-hrs/wk—continuous), red meat intake (medium servings per day—continuous), folate intake (μg/day—continuous), aspirin use (yes, no), diabetes (yes, no), education (less than high school graduate, high school graduate/some college, college graduate, post-college), ethnicity (White, Black, other), randomization status in each of the clinical trials (dummy variables for treatment, control, placebo, not randomized).

[b]HR2 adjusted for age, alcohol, pack-years, hormone therapy, family history of colorectal cancer, physical activity, red meat intake, folate intake, aspirin use, diabetes, education, ethnicity, randomization status.

[c]HR2 adjusted for age, alcohol, pack-years, hormone therapy, parity (continuous), age at menarche, age at first birth (<20, 20–29, ≥30, missing), age at menopause (<45, 45–54, ≥55, missing), family history of breast cancer in a first degree relative (yes, no, missing), history of breast biopsy (ever, never, missing), education, ethnicity, randomization status in clinical trials.

[d]HR2 adjusted for age, alcohol, pack-years, hormone therapy, parity, oral contraceptive use (ever, never), education, ethnicity, randomization status.

[e]HR2 adjusted for age, alcohol, pack-years, hormone therapy, oral contraceptive use (ever, never), education, ethnicity, and randomization status.

[f]Lower confidence limit = 1.001.

[g]HR2 adjusted for age, alcohol, pack-years, hormone therapy, education, ethnicity, and randomization status.

[h]HR2 adjusted for age, alcohol, pack-years, hormone therapy, age at menarche, education, ethnicity, and randomization status.

[i]HR2 adjusted for age, alcohol, pack-years, hormone therapy, history of thyroid nodules, history of goiter, education, ethnicity, and randomization status.

[j]HR2 adjusted for age, alcohol, hormone therapy, education, ethnicity, and randomization status.

linear growth (30). IGF-I has been shown to promote cell proliferation (31) and to inhibit apoptosis (32). In meta-analyses, circulating levels of IGF-I have shown modest positive associations with risk of prostate cancer, postmenopausal and premenopausal breast cancer, and colorectal cancer (33). Greater height may also be associated with increased exposure to steroid hormones and other growth factors (34). Exposures in adulthood that affect cancer risk (e.g., total energy consumption) may be associated with height due to their tracking from earlier life to adulthood. Another mechanism proposed to explain the association of height with cancer risk is that height may be

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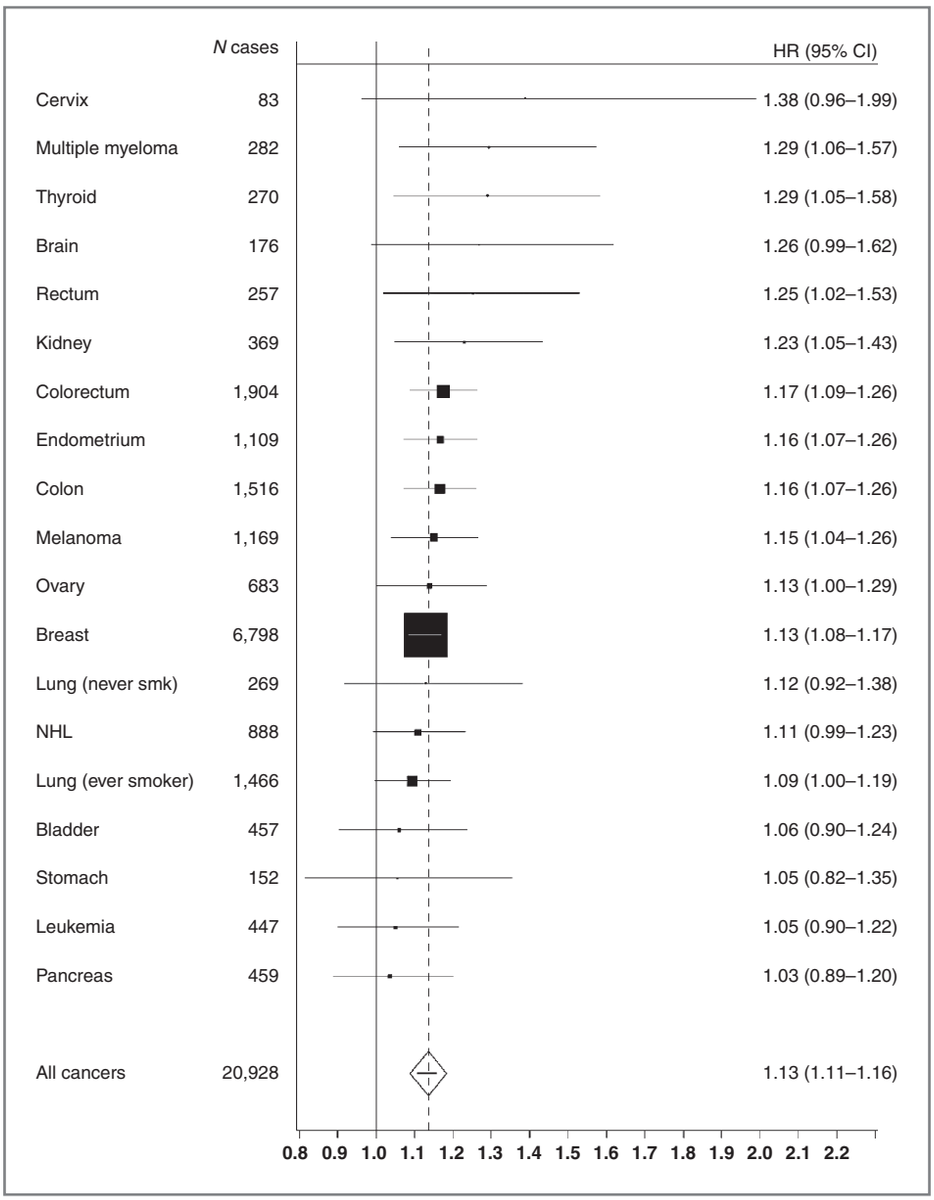

Figure 1. Association of height with all cancer and cancer at 19 anatomic sites. HR4s are adjusted for covariates in footnote h in Table 3.

associated with greater organ size and greater skin surface area, which may put more cells at risk of malignant transformation (35).

Based on studies of twins and siblings, height has a classic polygenic inheritance pattern (36). Eighty percent of the variation in height in Western populations is estimated to be determined by genetics (36). Genome-wide association studies have identified at least 180 single nucleotide polymorphisms (SNP) associated with height in humans (37, 38). The association between height and cancer risk that we report here might be explained if SNPs associated with height, or SNPs in linkage disequilibrium with these SNPs, are deemed functional and predispose men and women to cancer. SNPs in α-ketoglutarate–dependent dioxygenase have been associated with both height and endometrial cancer risk (39, 40). The biologic impact of SNPs associated with height is potentially far-reaching. For example, SNPs linked to LIN28B have been recently associated with ovarian cancer susceptibility (41). High levels of LIN28 expression have been reported in primordial germ cells, where they maintain pluripotency by inhibiting let-7 miRNA biogenesis (42). In the female reproductive tract, LIN28 has been implicated in both ovarian development as well as the subsequent timing of menarche, an important determinant of height in girls (43, 44). Although expression of LIN28 is tightly repressed in most adult somatic tissues, dysregulated expression of both LIN28A and LIN28B has been reported in seemingly unrelated human tumors, including cancers of the colon, lung, breast, thyroid, and leukemia (45–51).

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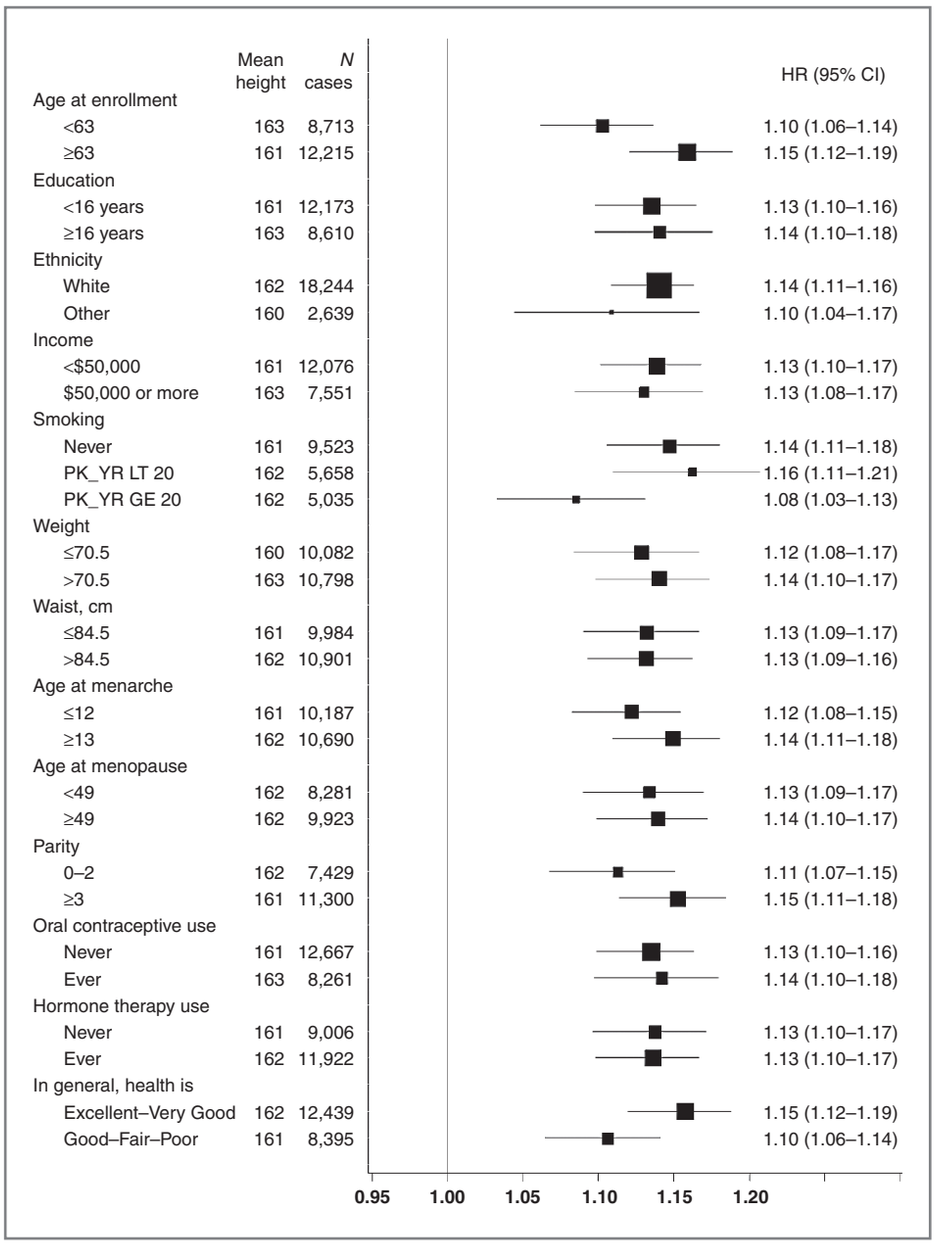

Figure 2. Association of height with risk of all cancers by level of potential effect modifiers. HR4s are adjusted for covariates in footnote h in Table 3.

Our study has a number of strengths including its prospective design, measurement of height and weight by trained study staff according to a standard protocol, the large number of incident cancer cases, the central adjudication of outcomes, and detailed information collected at baseline on a wide variety of potential risk factors and modifying factors. In addition, we adjusted for body weight using the scaling of W/H^X that was least associated with height to minimize potential confounding due to the correlation between height and weight. Limitations include the fact that we could not assess the association of height with cancer risk in men or in premenopausal women. In addition, measurements of 2 components of height—leg length and sitting height—which are considered more specific biomarkers of growth hormone exposure than height in prepuberty and postpuberty, respectively, were not available in our study (52). Finally, we did not have information on all relevant confounding variables, such as risk factors for melanoma (skin color, eye color, hair color, sun exposure).

In conclusion, in this large prospective cohort of postmenopausal women adult height showed a modest but statistically significant positive association with risk of any cancer and with risk of melanoma, multiple myeloma, and cancers of the thyroid, ovary, rectum, breast, colorectum, and endometrium. In addition, the association of height with cancers of the colon, cervix, brain, NHL, and lung (ever smokers) bordered on statistical significance.

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These associations were not explained by confounding by known risk factors, and there was little suggestion of effect modification by a large number of other risk factors. It is interesting to note that the number of cancer sites/types associated with height in the WHI is considerably larger than the number associated with BMI (13). Further elucidation of the function of the genetic loci associated with height may help to clarify possible mechanisms underlying the associations of height with specific cancers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Development of methodology: G.C. Kabat, T.E. Rohan

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): G.C. Kabat, D.S. Lane, J. Wactawski-Wende, J.E. Manson

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): G.C. Kabat, M.L. Anderson, M. Heo, D.H. Hosgood, V. Kamensky, J.W. Bea, L. Hou, J.E. Manson, T.E. Rohan

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): G.C. Kabat, J.E. Manson

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Adult Stature and Risk of Cancer at Different Anatomic Sites in a Cohort of Postmenopausal Women

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