Body Size, Physical Activity, and Risk of Hodgkin's Lymphoma in Women

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Abstract

Few studies have examined the associations of body size and physical activity with the development of Hodgkin's lymphoma (HL) in women. In data from a population-based case-control study in women ages 19 to 79 years, we assessed the relation of self-report height, weight, body mass index (BMI), and strenuous physical activity to HL risk in 312 cases with diagnostic re-review and 325 random-digit dialed controls using logistic regression. Analyses were stratified by age group and tumor cell presence of EBV. After adjustment for social class measures, taller childhood and adult height were associated with higher HL risk. In women ages 19 to 44 years, HL risk was elevated for higher, but healthy, BMI values, whereas in women ages 45 to 79 years, associations with BMI were inverse. The odds of developing HL were lower with participation (versus nonparticipation) in strenuous physical activity in the past year [odds ratio (OR), 0.58; 95% confidence interval (95% CI), 0.39-0.87 in women 19-44 years; OR, 0.45; 95% CI, 0.19-1.06 in women 45-79 years] and throughout adult life, and with sports team membership (versus nonmembership) in high school and/or at ages 18 to 22 years. Results were similar in cases (n = 269) with and without tumor-cell EBV compared with controls, although the inverse association with physical activity was somewhat stronger for women with EBV-positive disease. These findings show that in women, body size and strenuous physical activity, both modifiable characteristics, are associated with HL risk in adult life possibly through immunologic, infectious, or genetic mechanisms. (Cancer Epidemiol Biomarkers Prev 2006;15(6):1095–101)

Introduction

Hodgkin's lymphoma (HL) is a lymphoid malignancy that is one of the most common cancers of young adults (1). Although its etiology is far from established, epidemiologic studies have implicated an infectious precursor, EBV (2, 3), as well as identified generally consistent associations with higher social class, selected reproductive factors, familial aggregation, genetic factors, and certain occupations (2-4). Scattered studies have suggested that taller height (5-8) and higher body mass index (BMI) in men (9, 10), but not women (10-12), affect risk of HL. Furthermore, in the single previous study of physical activity and HL risk, participation in intramural or varsity sports ≥5 hours per week early in college was associated with a nonsignificantly reduced risk of HL (13). Body size and physical activity, shown to be related to various malignancies including other lymphomas (10, 14, 15), are known to influence immune function (16-18), which is likely critical in HL etiology. Thus, a role of these factors in HL development would be consistent with its epidemiology as currently understood. However, few prior HL studies examined these associations in detail or with attention to social class confounding, and data have been particularly limited for women.

The objective of this study was to assess the relation of height, weight, BMI, and strenuous physical activity to the development of HL in women using data from a population-based case-control study of the effect of reproductive factors on HL risk.

Materials and Methods

For the case-control study, detailed elsewhere (4, 19, 20), the population-based Greater Bay Area Cancer Registry identified 395 women ages 19 to 79 years and living in the Greater Bay Area of northern California when newly diagnosed with HL between mid July 1988 and the end of December 1994. Institutional review boards at the Northern California Cancer Center and Stanford University approved this project and its informed consent procedures. Among the 377 eligible HL patients (i.e., those alive at report to the registry), 320 (85%) were interviewed. Response rates were lower in women over age 54 years (53%), primarily due to mortality. The median time from diagnosis to interview for cases was 13 months, as it generally took ~12 months for cases to be reported to the cancer registry. Histopathologic re-review confirmed that 312 patients had HL, and these women were included in this study. They were predominantly young (mean age at diagnosis = 35.0 years) and composed of 251 non-Hispanic whites (80%), 26 blacks (8%), 18 Hispanics (6%), and 17 Asians (5%). Controls were women without a history of HL, living in the same geographic area, identified through random-digit dialing, and frequency matched to cases on 5-year age group and race/ethnicity; of the 450 invited into the study, 325 (72%) participated.

Subjects were interviewed with a standardized instrument in person or by phone (for the 30 women who had moved out

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of the area) about reproductive factors and exposure to exogenous hormones, as well as about social class characteristics considered potential confounders for these associations, for a reference period corresponding to the year before diagnosis for cases and the same time before interview for controls. In addition, subjects were asked to estimate their height relative to their peers (taller, the same, or shorter) at ages 8 and 12 years, their height in feet and inches at age 21 years, or at interview if 19 to 20 years old, and their weight in pounds and ounces at birth and at the reference period. Birth weight was missing for 21% of subjects ages 19 to 44 years and 36% of subjects ages 45 to 79 years; women with missing data were more likely to be non-white but did not differ on any other characteristic measured including case-control status, presence of EBV in HL tumors, and the body size/physical activity variables (as described below). As regards physical activity, each subject was asked about the annual number of months (none, 1-3, 4-6, 7-9, or 10-12) she participated in strenuous physical activities or sports that caused her ''to get out of breath or to work up a sweat'' at least twice weekly during high school, from ages 18 through 22 years, at ages 25, 35, and 50 years, and at the reference period. For each time period, the referent group included women who were inactive at that time period. Subjects also were asked whether they participated as a member of a sports team or group (outside of physical education classes) in high school and/or from ages 18 through 22 years. The physical activity questions were taken from an instrument used by the College Alumni Health Study (21).

Adult height and weight at the reference period (converted to meters and kilograms) were categorized into quartiles based on distributions in the control group and combined to create BMI (kg/m^2); obesity was defined as a BMI >30.0 kg/m^2 and overweight was defined as 25.0 to 29.9 kg/m^2 based on the WHO designations (22). Because most young adult subjects had BMIs in the reference range (<25.0 kg/m^2), we also considered quartiles of BMI based on the distribution of controls in this age group. To summarize strenuous physical activity throughout adulthood, we categorized women as ''active'' if they participated in strenuous physical activities or sports at least twice a week for at least 1 month per year at all of the times queried, and inactive otherwise.

EBV, an established oncogenic herpesvirus, has been detected in the tumor cells of some HL patients (2, 3, 23), and HL epidemiology varies by EBV tumor-cell presence (24-26). Therefore, we (R.F.A., R.B.M., and J.AD.) tested for tumor-cell EBV using *in situ* hybridization for EBV RNA (EBER1), with positive and negative controls, and standard immunohistochemical assays for EBV protein (LMP1), as described elsewhere (27, 28), in paraffin-embedded tissue sections from the 311 HL patients (79% of 395) for whom usable pathology specimens could be retrieved. Among the 269 patients with known EBV tumor status and interview data, and therefore eligible for inclusion in these analyses, 37 (14%) had EBV-positive tumors, including 11% of women ages <45 years and 23% of women ages ≥45 years; 11% of non-Hispanic whites and 25% of all others; and 10% of the nodular sclerosis histologic subtype cases and 43% of mixed cellularity cases.

Statistical Analysis. Associations between HL and each body size and physical activity measure were first examined by descriptive statistics, including quartiles for continuous variables. These analyses were stratified by age at diagnosis grouped as 19 to 44 years (young adults) and 45 to 79 years (older adults), on the basis of regional age-specific incidence patterns, and showed differences in risk factor patterns (1, 19, 20). Within each of these two age groups, data were further examined by tumor EBV presence, race/ethnicity, and other factors. Using unconditional logistic regression, we computed odds ratios (OR) and corresponding 95% confidence intervals (95% CI) to estimate relative risks of HL associated with each variable under study. The ORs were adjusted for variables previously determined to be associated with HL (4, 19, 20, 29); these included age in years, race/ethnicity (white, nonwhite), cigarette smoking 1 year before diagnosis/interview (current, former, never), ever having nursed children, number of miscarriages (0, 1, and 2+), having a first- or second-degree family history of lymphoma, Jewish heritage, having a single room at age 11 years, and living in a rented family home at age 8 years. Heterogeneity between age groups was assessed with a Wald test of the significance of an interaction term between age group (young or older) and each variable of interest, coded categorically. Monotonic trends were assessed with a Wald test of the significance of the variable of interest coded ordinally using the median value of each category.

Results

Body Size. Among young adult women, 73% of cases and 63% of controls providing birth weight data had a self-reported birth weight <3.6 kg. At the reference period, cases and controls had mean weights of 63.8 and 62.8 kg, respectively, and mean heights of 1.66 and 1.65 m, respectively. For 76% of cases and 79% of controls, BMI was in the reference range. Table 1 shows that, for young adults, weight was related to risk of HL suggestively at birth, even after adjustment for BMI (data not shown), but not in adulthood after adjustment for height. In contrast, taller height in childhood and adulthood were related to HL, even after control for various socioeconomic measures and for adult weight (the latter data not shown). Risk of HL was nonsignificantly increased for women who reported being the same height as or taller than most other girls at age 12 years, as compared with being shorter; results were similar for height at age 8 years (data not shown). Adult height in the third and fourth quartiles compared with the first quartile was linked to an increased risk of HL. Similarly, women in higher BMI quartiles, particularly the second and fourth quartiles, had increased risks of HL compared with women in the first quartile of BMI. Being overweight at the reference period also was marginally associated with increased risk of HL ($P = 0.07$). Being obese was not associated with HL risk, although these findings were based on only 19 obese cases and 22 obese controls.

Among older women, 68% of cases and 86% of controls providing birth weight data had a birth weight of <3.6 kg. At the reference period, cases and controls had mean weights of 68.8 and 68.3 kg, respectively, and mean heights of 1.65 and 1.64 m, respectively. For 66% of cases and 52% of controls, BMI was in the reference range. Table 1 shows that, in this older age group, the risk of HL was significantly reduced for women at higher weight at birth, even after adjustment for baseline BMI (data not shown), and lower, albeit not significantly, for heavier women in adulthood after adjustment for height. However, the relationships between HL and birth weight or adult weight were not significantly different from the relationships in younger women, likely due to the small numbers of older adults. In older adults, height in childhood and in adulthood showed associations with HL similar to those in young adults, although none were statistically significant. Higher BMI was associated with a lower risk of HL, but again not significantly. Being overweight, but not obese, compared with having a normal weight at the reference period was associated with a lower risk of HL. The relationship of being overweight, versus normal weight, with risk of HL was significantly different between older and younger women ($P = 0.02$).

Physical Activity. Among young adult women, being strenuously physically active throughout adult life was

Table 1. Adjusted ORs (95% CIs) for the association between height and weight and risk of Hodgkin's lymphoma among women 19 to 44 and 45 to 79 years of age

Characteristic	Women 19-44 y			Women 45-79 y		
	Cases (*n*), *N* = 253	Controls (*n*), *N* = 254	Adjusted* OR (95% CI)	Cases (*n*), *N* = 59	Controls (*n*), *N* = 71	Adjusted* OR (95% CI)
Birth weight, kg						
1st, <2.78	53	76	Reference	13	6	Reference
2nd, 2.78 to <3.63	82	73	1.59 (0.96-2.63)	14	18	0.19 (0.04-0.98)
3rd, ≥3.63	62	54	1.64 (0.95-2.82)	14	18	0.17 (0.03-0.91)
n missing	56	51	P_{trend} = 0.07	18	29	P_{trend} = 0.05
Adult weight, kg†						
1st, <54.9	65	74	Reference	9	6	Reference
2nd, 54.9 to <61.3	67	58	1.31 (0.77-2.21)	10	13	0.57 (0.12-2.75)
3rd, 61.3 to <69.0	63	67	1.09 (0.63-1.87)	21	25	0.56 (0.13-2.44)
4th, ≥69.0	58	54	1.18 (0.66-2.12)	19	27	0.35 (0.08-1.53)
n missing	—	1	P_{trend} = 0.74	—	—	P_{trend} = 0.15
Height at age 12 y compared with most girls at this age						
Shorter	42	60	Reference	13	23	Reference
Same	120	110	1.51 (0.92-2.48)	30	29	2.42 (0.85-6.86)
Taller	91	84	1.52 (0.90-2.56)	15	18	1.63 (0.52-5.14)
n missing	—	—	P_{trend} = 0.16	1	1	P_{trend} = 0.41
Adult height, m						
1st, <1.60	33	51	Reference	11	22	Reference
2nd, 1.60 to <1.65	58	71	1.13 (0.62-2.04)	13	12	2.41 (0.66-8.76)
3rd, 1.65 to <1.70	72	58	2.06 (1.13-3.76)	19	19	3.15 (0.96-10.30)
4th, ≥1.70	90	74	1.98 (1.11-3.54)	16	18	2.21 (0.68-7.19)
n missing	—	—	P_{trend} = 0.01	—	—	P_{trend} = 0.21
BMI, kg/m^2‡						
1st	52	65	Reference	18	16	Reference
2nd	76	62	1.96 (1.15-3.32)	16	20	0.64 (0.21-1.94)
3rd	58	63	1.36 (0.79-2.35)	13	17	0.61 (0.19-1.99)
4th	67	63	1.74 (1.00-3.02)	12	18	0.37 (0.11-1.30)
n missing	—	1	P_{trend} = 0.20	—	—	P_{trend} = 0.14
BMI, kg/m^2						
Normal, <25	192	199	Reference	39	37	Reference
Overweight, 25 to <30	42	32	1.66 (0.96-2.86)	9	21	0.33 (0.12-0.96)
Obese, ≥30	19	22	0.84 (0.42-1.70)	11	13	0.51 (0.16-1.63)
n missing	—	1	P_{trend} = 0.71	—	—	P_{trend} = 0.11

*Adjusted for continuous age, race/ethnicity (white versus non-white), education (high school or less versus greater than high school), Jewish upbringing, having a single room at age 11 years, living in a single family home at age 8 years, living in a rented family home at age 8 years, having ever nursed children, number of miscarriages (0, 1, 2+), smoking status 1 year before diagnosis/interview, and history of first- or second-degree relative with lymphoma.

†Adjusted for height in inches in addition to the variables mentioned above.

‡BMI quartiles in young adults: 1st (<19.9), 2nd (19.9 to <21.7), 3rd (21.7 to <24.5), and 4th (≥24.5); BMI quartiles in older adults: 1st (<22.3), 2nd (22.3 to <24.2), 3rd (24.2 to <29.1), and 4th (≥29.1).

associated with a nonsignificantly reduced risk for HL whereas participating in strenuous physical activity at least twice a week for ≥1 months before the reference period led to an ~40% reduction in the odds of HL (Table 2). Among women who reported exercising strenuously before the reference period, the largest single proportion (49%) exercised for 10 to 12 months per year; the risk of HL was similarly reduced for women who participated in strenuous physical activity for varying amounts of time during this time period (data not shown). Among the 53% of all young adult women eligible based on attained age to report their activity levels at age 25 years, risk was similarly reduced for those participating in strenuous activity (OR, 0.75; 95% CI, 0.43-1.30); participation in activity at age 35 years could not be reliably assessed because only 13% of young adult women were old enough at interview to answer this question. Regular participation in a sports team or group at the ages of 18 to 22 years was associated with a reduced risk of HL. Adjustment of the physical activity measures at different time points for all related variables (participation in strenuous physical activity in the past year, having been a member of a sports team or group in high school, and having been a member of a sports team or group at ages 18-22 years) did not alter the ORs substantially (data not shown).

In older women (Table 2), none of the physical activity measures was significantly associated with HL, although all point estimates of the OR were below unity. As with young women, most women (73%) who exercised strenuously before the reference period exercised for 10 to 12 months per year, and the risk of HL was similarly reduced for women who participated in strenuous physical activity at least twice a week for varying lengths of time before the reference period (data not shown). HL risk was not consistently associated with participation in strenuous physical activity at ages 25, 35, or 50 years in older women (data not shown).

Associations for EBV-Positive and EBV-Negative HL. The associations between body size or physical activity measures and HL risk did not seem to vary markedly by EBV presence in the tumor cells in young women (Table 3). However, associations of risk with adult height were slightly stronger and statistically significant only for EBV-negative HL (compared with all controls) whereas associations with strenuous physical activity seemed to be slightly stronger for EBV-positive HL. The small numbers of older women with EBV positive tumors (*n* = 13) limited our ability to assess associations in this age group (data not shown).

Associations by Race/Ethnicity. In young adults, the relationships between body size and physical activity measures and HL risk did not significantly differ between whites (*n* = 204 cases; *n* = 204 controls) and non-whites (*n* = 49 cases; *n* = 50 controls), although the relationship between taller height and HL was stronger in non-whites, as previously reported (20). With the reference group of women <1.60 m

in height, the adjusted OR (with 95% CI) for HL was 2.85 (0.89-9.11) in non-whites and 0.93 (0.46-1.87) in whites 1.60 to <1.65 m tall; 2.46 (0.63-9.68) in non-whites and 1.76 (0.89-3.47) in whites 1.65 to <1.70 m tall; and 6.57 (1.52-28.47) in non-whites and 1.62 (0.84-3.12) in whites ≥1.70 m tall. In older women, the small numbers of non-whites (n = 12 cases; n = 12 controls) precluded reliable statistical analyses.

Discussion

Our study found associations of HL risk with various measures of body size, including height and BMI, and strenuous physical activity, even after adjustment for measures of childhood and adult social class. Whereas taller height was associated with a higher risk of HL in all women, the association between higher BMI and HL risk varied by age, with higher BMI conferring an increased risk in younger women and a decreased risk in older women. In addition, strenuous physical activity at various time points in adult life was consistently associated with a reduced risk of HL in women in both age groups.

Higher birth weight also seemed to increase HL risk in young adults and reduce the risk in older adults. The single previous study of infant and childhood weight and HL risk reported that HL patients were significantly heavier at birth and at ages 10 and 12 years than controls matched on age, sex, and social class (5). In addition, our findings of a positive association of taller childhood and adult height with risk of HL are consistent with prior studies of males and females, in whom HL has been associated with taller height in childhood (5, 6), especially at ages 10 and 12 years (5), at age >13 years (6), and in adulthood (7, 8). However, two studies (9, 30) did not find an association between height and HL risk.

Higher BMI, including levels considered healthy by the WHO (<25 kg/m^2), was linked to elevated HL risk in young women, although there was no apparent trend toward increasing HL risk with higher quartiles of BMI. In contrast, for older women, being overweight was associated with a lower risk of HL. The few previous studies of BMI with HL risk found no association in women (10-12) but two studies (9, 10) found an association between obesity and HL in men. In a nested case-control study of college alumni, men who were overweight or obese at baseline had an almost 2-fold increased risk of HL compared with living age-matched classmates (9). In persons with a hospital discharge of obesity (defined as BMI ≥28.6 kg/m^2), males had a 3-fold higher incidence of HL whereas women (for whom obesity was defined as a BMI ≥30.0 kg/m^2) did not have an elevated incidence of HL (10).

Recent strenuous physical activity, as well as sports team membership at ages 18 to 22 years, was associated with decreased risks for HL significantly in young adult women and nonsignificantly in older women. Strenuous activity throughout adult life also was associated with a nonsignificantly reduced risk of HL and significantly reduced risk of the EBV-positive variant in young adults. To our knowledge, the association between physical activity and HL risk has been examined in only one prior study (13). In a cohort of college students, participation in intramural or varsity sports ≥5 hours per week early in college was associated with a nonsignificantly reduced risk of developing HL during follow-up (age- and sex-adjusted hazard ratio, 0.73; P = 0.34; ref. 13). However, this study was unable to assess potential social class confounding characteristics or the level of physical activity in later life as it might relate to HL risk.

Most exposures previously tied to HL risk in women involve childhood infection or adult reproductive experiences (3, 4, 31). Based on these associations and present ideas about HL etiology, anthropometric measures and physical activity could be related to HL pathogenesis through mechanisms involving the immune response and/or steroid or metabolic hormone functions, although the pathways through which these factors may affect lymphoma development remain poorly understood. Physical activity could reduce HL risk by increasing the activity of natural killer cells (15, 32, 33) or by reducing inflammation (34). It also could decrease bioavailable insulin and insulin-like growth factors (15, 16), which stimulate cell turnover in most tissues and inhibit cell death (16, 32), and/or levels of endogenous sex hormones (16, 32, 33), which may affect HL pathogenesis indirectly through their influences on immune function (35). If, as suggested by some previous studies, EBV-positive HL patients have disordered immunity relative to EBV-negative HL patients (36, 37) and controls (38), then the effects of physical activity on immune function could be more beneficial toward the prevention of EBV-positive HL. Higher BMI may be associated with a higher

Table 2. Adjusted ORs (95% CIs) for the association between strenuous physical activity and sports participation and risk of Hodgkin's lymphoma among women 19 to 44 and 45 to 79 years of age

Characteristic	Women 19-44 y			Women 45-79 y		
	Cases (n), N = 253	Controls (n), N = 254	Adjusted* OR (95% CI)	Cases (n), N = 59	Controls (n), N = 71	Adjusted* OR (95% CI)
Participated in strenuous physical activity at least twice a week for ≥1 mo throughout life						
Yes	116	133	0.71 (0.48-1.05)	6	11	0.35 (0.09-1.36)
No	137	121	Reference	53	60	Reference
n missing	—	—		—	—	
Participated in strenuous physical activity at least twice a week for ≥1 mo in the past year						
Yes	149	179	0.58 (0.39-0.87)	26	41	0.45 (0.19-1.06)
No	103	74	Reference	33	30	Reference
n missing	1	1		—	—	
Member of a sports team or group in high school						
Yes	127	144	0.75 (0.51-1.10)	16	24	0.87 (0.34-2.28)
No	120	103	Reference	37	42	Reference
n missing	6	7		6	5	
Member of sports team or group at ages 18-22 y						
Yes	50	74	0.57 (0.36-0.90)	5	13	0.34 (0.08-1.48) †
No	162	131	Reference	31	28	Reference
n missing	41	49		23	30	

*Adjusted for continuous age, race/ethnicity (white versus non-white), education (high school or less versus greater than high school), Jewish upbringing, having a single room at age 11 years, living in a single family home at age 8 years, living in a rented family home at age 8 years, having ever nursed children, number of miscarriages (0, 1, 2+), smoking status 1 year before diagnosis/interview, and history of first- or second-degree relative with lymphoma.
† Adjusted for all the variables mentioned above except history of first- or second-degree relative with lymphoma.

risk for HL, at least in younger women, via the same biological mechanisms. In particular, high BMI could influence risk of HL by triggering higher levels of the cytokine interleukin-6 (39), insulin resistance, compensatory hyperinsulinemia, or increased production of growth factors, including estrogens (14); all of these mechanisms are thought to be important for other, mostly reproductive, malignancies in women. Our unexpected finding that being overweight reduces the risk for HL in older women is difficult to explain biologically. Given that response rates were lower in older cases due, in part, to poorer survival and that HL survival seems to be influenced by BMI (40), it is possible that our results in older women are biased due to selection for surviving HL cases with higher BMI.

The relationship between taller adult height and elevated risk for HL could involve several mechanisms. First, nascent HL tumors may be promoted by higher circulating levels of insulin-like growth factors and other growth hormones in taller women (41, 42). In one study, patients treated during childhood and early adulthood with human pituitary growth hormone, which raises the serum concentration of insulin-like growth factors, had 11-fold higher risks of HL mortality compared with the general population, although this finding was based on only two cases of HL (43). Height and HL could

Table 3. Adjusted ORs (95% CIs) for the association between height, weight and physical activity and risk of Hodgkin's lymphoma by EBV presence in the tumor cells among women 19 to 44 years of age

Characteristic	EBV positive			EBV negative		
	Cases (n), N = 24	Controls (n), N = 254	Adjusted* OR (95% CI)	Cases (n), N = 187	Controls (n), N = 254	Adjusted† OR (95% CI)
Birth weight, kg						
1st, <2.78	4	76	Reference	38	76	Reference
2nd, 2.78 to <3.63	11	73	3.27 (0.91-11.71)	62	73	1.75 (1.01-3.04)
3rd, ≥3.63	5	54	1.97 (0.46-8.49)	45	54	1.76 (0.97-3.19)
n missing	4	51	P_{trend} = 0.35	42	51	P_{trend} = 0.06
Adult weight, kg‡						
1st, <54.9	7	74	Reference	48	74	Reference
2nd, 54.9 to <61.3	6	58	1.11 (0.33-3.75)	44	58	1.17 (0.66-2.08)
3rd, 61.3 to <69.0	5	67	0.91 (0.24-3.41)	50	67	1.14 (0.64-2.03)
4th, ≥69.0	6	54	0.92 (0.24-3.53)	45	54	1.26 (0.67-2.36)
n missing	—	1	P_{trend} = 0.85	—	1	P_{trend} = 0.49
Height at age 12 y compared with most girls at this age						
Shorter	3	60	Reference	33	60	Reference
Same	14	110	1.39 (0.33-5.84)	89	110	1.51 (0.88-2.58)
Taller	7	84	2.13 (0.56-8.05)	65	84	1.45 (0.83-2.54)
n missing	—	—	P_{trend} = 0.85	—	—	P_{trend} = 0.26
Adult height, m						
1st, <1.60	3	51	Reference	23	51	Reference
2nd, 1.60 to <1.65	7	71	1.13 (0.25-5.13)	43	71	1.26 (0.65-2.46)
3rd, 1.65 to <1.70	7	58	1.82 (0.39-8.44)	59	58	2.45 (1.26-4.73)
4th, ≥1.70	7	74	1.52 (0.33-7.07)	62	74	2.01 (1.05-3.85)
n missing	—	—	P_{trend} = 0.58	—	—	P_{trend} = 0.03
BMI, kg/m^2						
Normal, <25	18	199	Reference	140	199	Reference
Overweight, 25 to <30	1	32	0.29 (0.03-2.47)	34	32	1.93 (1.08-3.45)
Obese, ≥30)	5	22	2.06 (0.60-7.04)	13	22	0.84 (0.39-1.81)
n missing	—	1	P_{trend} = 0.43	—	1	P_{trend} = 0.56
BMI, kg/m^2						
1st, <19.9	4	65	Reference	37	65	Reference
2nd, 19.9 to <21.7	9	62	2.74 (0.77-9.76)	57	62	2.02 (1.14-3.59)
3rd, 21.7 to <24.5	5	63	1.38 (0.34-5.68)	41	63	1.28 (0.71-2.33)
4th, ≥24.5	6	63	1.34 (0.32-5.67)	52	63	1.94 (1.07-3.54)
n missing	—	1	P_{trend} = 0.91	—	1	P_{trend} = 0.12
Participated in strenuous physical activity at least twice a week for ≥1 mo throughout adult life						
Yes	7	133	0.34 (0.12-0.93)	83	133	0.66 (0.43-1.01)
No	17	121	Reference	104	121	Reference
n missing	—	—		—	—	
Participated in strenuous physical activity at least twice a week for ≥1 mo in the past year						
Yes	10	179	0.33 (0.13-0.81)	110	179	0.56 (0.37-0.86)
No	14	74	Reference	76	74	Reference
n missing	—	1		1	1	
Member of a sports team or group in high school						
Yes	26	144	0.82 (0.33-2.03)	88	144	0.68 (0.45-1.03)
No	16	103	Reference	94	103	Reference
n missing	1	7		5	7	
Member of sports team or group at ages 18-22 y						
Yes	1	74	0.07 (0.01-0.53)	36	74	0.57 (0.35-0.94)
No	17	131	Reference	117	131	Reference
n missing	6	49		34	49	

NOTE: EBV presence in tumor cells was assessed only among cases; EBV-positive and EBV-negative cases were compared with all controls in the age group.
*Adjusted for continuous age, race/ethnicity (white versus non-white), cigarette smoking status 1 year before diagnosis/interview, having a single room at age 11 years, living in a rented family home at age 8 years, and having ever nursed children.
†Adjusted for continuous age, race/ethnicity (white versus non-white), education (high school or less versus greater than high school), Jewish upbringing, having a single room at age 11 years, living in a single family home at age 8 years, living in a rented family home at age 8 years, having ever nursed children, number of miscarriages (0, 1, 2+), smoking status 1 year before diagnosis/interview, and history of first or second degree relative with lymphoma.
‡Adjusted for height in inches in addition to the variables above.

share common genetic determinants, as height is known to be influenced strongly by genes (41), and HL has been associated with genetic factors (44-46). In addition, taller height could reflect better nutrition (41, 47), which, like HL risk, is likely related to higher childhood socioeconomic status (2, 3). Similarly, the observed association of height and HL risk could reflect the effect of other uncontrolled socioeconomic factors, particularly given the stronger effect in nonwhites, for whom we previously showed stronger HL risks with several childhood socioeconomic characteristics (20). More frequent childhood exposure to infections, including *Helicobacter pylori*, may lead to ameliorated immune protection against HL while stunting growth (41, 42).

The strengths of our study include its population basis, uniformly re-reviewed histologic diagnoses, relatively high response rates, and detailed data to adjust for confounding. However, the study also has some limitations. First, risk factor data were self-reported and therefore subject to recall bias. Analyses of other variables from this data set (4) have not provided evidence of recall bias but it is possible that the findings for birth weight are biased, as one study found differential measurement error between breast cancer cases and controls despite the high correlation between self-reported and birth record birth weight (cases, $r = 0.83$; controls, $r = 0.80$; ref. 48). Second, our childhood height information was relative and provides only broad estimations of associated risk, although we considered it likely that respondents would recall their relative childhood height more accurately than their absolute height. Third, in certain age groups, controls were better educated than regional age- and race/ethnicity-specific census data would predict, although this bias was not large and had a small, mostly attenuating, effect on measures of association with social class and reproductive factors (49). Fourth, the association of strenuous physical activity 1 year before diagnosis with decreased risk could reflect reduced physical activity in patients due to symptoms of incipient HL. However, a lower risk for HL was noted among women who played sports in high school and during the ages of 18 through 22 years and exercised strenuously throughout adult life, suggesting that this inverse association with HL risk is not only attributable to prediagnostic changes in exercise patterns. Nevertheless, we cannot rule out the possibility of selection bias. Fifth, the measure created to summarize strenuous physical activity throughout life was inexact, as women could exercise as few as eight times per year in the years queried and still be considered active. However, in our study, women who were strenuously active at least 1 month tended to be active 10 to 12 months in each time period. Sixth, because this study only measured strenuous physical activity, we could not evaluate the combined or independent effect of less strenuous or occupational physical activity, alone or with strenuous physical activity, on HL risk at each time point or throughout life. Seventh, our study enrolled a small number of older women due to incidence patterns and the low response rate, primarily due to mortality. Thus, the effect of any risk factor also associated with survival would be underestimated in this age group. On the other hand, the finding that higher BMI was associated with lower risk for HL in older women may have resulted from BMI being related to survival (i.e., older women/cases with low BMI may be less likely to survive; ref. 40). Lastly, analyses of risks for EBV-related HL, involving the 79% of cases for whom specimens could be obtained, were affected by limited statistical power due to the low prevalence of EBV-positive HL in our study population (24, 26). To overcome these limitations, it would be ideal to examine the associations of body size and physical activity with risk of HL in a prospective cohort, although the low incidence of HL makes such a study design impractical for research on this lymphoma.

In conclusion, we have found that body size and strenuous physical activity are associated with HL risk in women. The positive associations of HL with higher childhood and adult height, which are consistent with previous findings, may suggest leads for future studies addressing HL risk associated with childhood nutrition and/or genetic susceptibility related to height; similarly, the novel findings of a higher risk of HL in young adults with higher, but healthy, BMI values and the opposite findings in older adults need further investigation. Our evidence that strenuous physical activity significantly reduces the risk of developing HL in women not only adds to the evidence in support for the health benefits of exercise but also may provide clues in the effort to elucidate HL pathogenesis in general, and for EBV-positive HL in particular. Better understanding of the associations of body size and physical activity with HL development will require exploring risks related to less strenuous and occupational physical activity, in addition to strenuous physical activity, at various time points and throughout life, and pursuing the biological mechanisms underlying any associations.

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