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Research Article

Association of Anthropometric Characteristics with the Risk of Malignant Lymphoma and Plasma Cell Myeloma in a Japanese Population: A Population-Based Cohort Study

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Abstract

Background: Although Asian and Western populations differ markedly in anthropometric characteristics and the incidence of malignant lymphoma and plasma cell myeloma, few studies have evaluated the associations between these variables among Asian populations.

Methods: We conducted a large-scale, population-based prospective study in a Japanese cohort that included 45,007 men and 49,540 women ages 40 to 69 years at baseline. During an average follow-up period of 13 years, 257 cases of malignant lymphoma and 88 of plasma cell myeloma were identified. Hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated with the use of a Cox regression model adjusted for potential confounders.

Results: Compared with the 1st quartile, categorization in the 4th quartile for height showed a positive association with lymphoid neoplasm risk (HR, 1.38; 95% CI, 1.00-1.91), and the association was significant among men (HR, 1.72; 95% CI, 1.11-2.66). A similar trend was observed for subcategories of malignant lymphoma, plasma cell myeloma, and non–Hodgkin lymphoma, albeit the associations were weak due to the small number of subjects in each category. In contrast, weight and body mass index were not associated with risk of lymphoid neoplasm.

Conclusions: Height was positively associated with risk of lymphoid neoplasm in a Japanese population.

Impact: Our data suggested that early life exposure to growth-related hormones, such as insulin-like growth factors and growth hormones, or genetic factors relating to height may affect the risk of lymphoid neoplasm. *Cancer Epidemiol Biomarkers Prev; 19(6); 1623–31. ©2010 AACR.*

Introduction

The increase in incidence of lymphoid neoplasms, including malignant lymphoma (ML) and plasma cell myeloma (PCL), in developed countries, including Japan, over the past several decades (1, 2) seems to have coincided with increases in height, weight, and body mass index (BMI) during the same period (3, 4). Whereas height is determined by genetic as well as environmental factors, such as nutritional status during childhood and adolescence, weight and BMI reflect nutritional status during adulthood as well. A number of case-control and cohort studies have evaluated associations between these anthropometric factors and risk of lymphoid neoplasms in Western populations (5-12). Although several of these showed a positive association between height and lymphoid neoplasm risk (5-9), others did not (10-12). Further, although a meta-analysis showed that obesity is a risk factor for non–Hodgkin lymphoma (NHL; ref. 13), a pooled analysis of 18 case-control studies conducted at various centers suggested no significant association between them (14). The association between these factors therefore remains unclear.

In contrast to the situation in Western populations, relatively few studies have been conducted in Asian populations. Epidemiologic research on ML and PCM in large Asian cohorts is particularly important, however, for the following reasons. First, Asian populations have different anthropometric characteristics and adiposity:

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Note: Japan Public Health Center–based Prospective Study Group: members are listed in the supplementary material.

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Table 1. Distribution of histologic subtypes in lymphoid neoplasms

Histologic subtype	ICD-O-3	Total, *n* (%)
ML		257
NHL		
Diffuse large B-cell lymphoma	9675(B), 9680, 9684	80 (23.2)
Follicular lymphoma	9690, 9691, 9695, 9698	18 (5.2)
Marginal zone B-cell lymphoma	9699	16 (4.6)
Precursor lymphoblastic leukemia/lymphoma	9835	11 (3.2)
Chronic lymphocytic leukemia/small lymphocytic lymphoma	9670, 9823	9 (2.6)
Peripheral T-cell lymphoma, unspecified	9702	5 (1.4)
Other NHLs	9673, 9687, 9689, 9700, 9705, 9709, 9714, 9718, 9719, 9832	13 (3.8)
NHL not otherwise specified	9591	53 (15.4)
Hodgkin lymphoma	9650, 9651, 9663	10 (2.9)
ML not otherwise specified	9590	42 (12.2)
PCM	9731, 9732	88 (25.5)
Total		345 (100)

Abbreviation: ICD-O-3, *International Classification of Diseases for Oncology*, 3rd edition.

the average height is lower in Asian than Western populations, and whereas BMI is generally lower, adiposity for a given BMI is higher (15). Second, the incidence of ML and PCM is substantially lower in Asian than Western countries (1): in Japan, for example, the respective age-adjusted incidence rates of ML and PCM in 2002 were 7.7 and 1.6 for men and 4.9 and 1.1 for women (16), or almost half of those in Western countries (1, 17). The distribution of histologic subtypes of ML differs in Asian and Western countries, with marginal zone B-cell lymphoma being more common, and Hodgkin lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma being rare (1, 18, 19). These differences in incidence and distribution indicate that epidemiologic background may differ between Asian and Western populations. Although recent cohort and case-control studies showed that height is associated with lymphoma risk in Asian populations (20, 21), no large case-control or cohort study specific to the association between height and risk of PCM has been conducted. Moreover, the results of the two cohort and one case-control studies of the association between obesity and lymphoma risk in Asia (21-23) were controversial.

Here, we investigate the association between anthropometric characteristics and risk of ML and PCM in a large-scale population-based cohort study in a Japanese population.

Materials and Methods

Study population

The design of the Japan Public Health Center–based Prospective Study has been detailed elsewhere (24, 25). Briefly, the Japan Public Health Center–based Prospective Study was launched in 1990 for Cohort I and in 1993 for Cohort II, covering five and six prefectural public health center areas, respectively. The study protocol was approved by the Institutional Review Board of the National Cancer Center, Japan. At the start of the respective baseline surveys, the study population included all registered Japanese inhabitants ages 40 to 59 years in the public health center areas in Cohort I and those ages 40 to 69 years in the public health center areas in Cohort II. In the present analysis, all subjects in one public health center area were excluded because their incidence data were not available, and some subjects in another area were also excluded because different definitions of the study population had been applied. Initially, we identified 123,468 subjects as study population. During the follow-up period, 230 subjects were excluded because of non-Japanese nationality (n = 51), late report of emigration before the start of the follow-up period (n = 166), incorrect birth date (n = 3), duplicate registration (n = 4), and eventual withdrawal of consent (n = 6), leaving a final total of 123,238 subjects.

We conducted a baseline self-administered questionnaire survey on various lifestyle and anthropometric factors in 1990 for Cohort I and in 1993 to 1994 for Cohort II, with a high response rate (n = 99,662; 80.9%). Subjects who reported a previous incidence of cancer in the questionnaire (n = 2,134) and those for whom details of anthropometric characteristics, alcohol intake, or smoking status could not be obtained (n = 2,981) were excluded. Finally, a total of 94,547 subjects (45,007 men and 49,540 women) were included in the analysis.

Exposure data

Four indicator variables (1st-4th quartiles) of height and weight were created separately in men and women with the use of quartiles based on the distribution of male and female subjects. The subjects included in each

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Table 2. Baseline characteristics of study subjects by height, weight, and BMI

	Height*				Weight†				BMI (kg/m^2)				
	1st quartile	2nd quartile	3rd quartile	4th quartile	1st quartile	2nd quartile	3rd quartile	4th quartile	<18.5	18.5-22.9	23.0-24.9	25.0-29.9	30.0≤
Men (*n* = 45,007)													
No. of subjects	13,881	9,778	11,299	10,049	12,071	12,306	9,889	10,741	1,233	18,830	12,439	11,560	945
Proportion (%)	30.8	21.7	25.1	22.3	26.8	27.3	22.0	23.9	2.7	41.8	27.6	25.7	2.1
Age (y) ± SD	54.7 ± 7.7	52.2 ± 7.8	50.8 ± 7.7	48.8 ± 7.4	54.2 ± 8.2	52.3 ± 7.9	50.9 ± 7.6	49.7 ± 7.2	54.3 ± 9.0	52.3 ± 8.2	51.7 ± 7.8	51.1 ± 7.5	50.6 ± 7.3
Alcohol intake (%)													
Nondrinkers and occasional drinkers	35.6	33.0	31.1	28.0	34.5	31.2	30.6	31.7	40.6	31.5	30.9	33.2	39.7
1-149 g/wk	21.4	23.3	23.0	24.0	21.7	23.7	23.9	22.0	21.3	23.1	23.5	22.2	17.3
150-299 g/wk	19.3	19.6	20.6	20.8	19.4	20.3	20.7	19.8	17.4	20.2	20.7	19.8	15.6
≥300 g/wk	23.7	24.0	25.4	27.2	23.9	24.9	24.7	26.5	20.8	25.2	24.9	24.8	27.5
Smoking status (%)													
Never	27.4	24.2	22.4	20.9	21.0	23.6	25.9	26.2	17.0	20.3	25.4	28.9	30.0
Former	24.1	24.9	24.3	22.0	21.0	23.9	25.4	25.5	19.5	21.2	25.8	26.4	26.7
Current	48.4	50.9	53.3	57.1	57.9	52.5	48.7	48.3	63.8	58.5	48.8	44.8	43.4
Women (*n* = 49,540)													
No. of subjects	13,268	14,874	9,604	11,794	13,487	11,534	12,901	11,618	1,754	21,628	12,046	12,514	1,598
Proportion (%)	26.8	30.0	19.4	23.8	27.2	23.3	26.0	23.5	3.5	43.7	24.3	25.3	3.2
Age (y) ± SD	55.1 ± 7.9	52.7 ± 7.8	51.1 ± 7.7	49.7 ± 7.5	53.1 ± 8.5	52.1 ± 8.0	52.0 ± 7.8	51.9 ± 7.7	53.1 ± 8.8	51.6 ± 8.2	52.3 ± 7.8	53.2 ± 7.7	53.2 ± 7.7
Alcohol intake (%)													
Nondrinkers and occasional drinkers	91.8	89.1	87.6	84.6	88.8	87.9	87.9	89.2	87.3	86.9	89.0	90.3	92.4
1-149 g/wk	6.6	8.7	9.9	12.2	8.9	9.8	9.8	8.2	9.8	10.4	9.1	7.5	5.6
150-299 g/wk	0.9	1.3	1.6	2.0	1.5	1.4	1.3	1.5	1.8	1.7	1.1	1.4	1.0
≥300 g/wk	0.7	0.9	0.9	1.3	0.9	0.8	1.0	1.0	1.1	0.9	0.9	0.9	1.0
Smoking status (%)													
Never	93.9	93.0	92.2	90.3	91.7	93.2	93.2	91.8	87.6	92.0	93.9	92.8	89.8
Former	1.2	1.5	1.3	1.9	1.4	1.1	1.5	1.9	1.7	1.4	1.4	1.7	2.1
Current	4.9	5.5	6.5	7.8	7.0	5.7	5.3	6.3	10.7	6.6	4.7	5.6	8.1

*The ranges of each quartile for height were 115-160, 161-164, 165-168, and 169-199 cm for men, and 110-148, 149-152, 153-155, and 156-198 cm for women.
†The ranges of each quartile for weight were 30-57, 58-63, 64-69, and 70-115 kg for men, and 27-49, 50-53, 54-59, and 60-98 kg for women.

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Table 3. HRs and 95% CIs of lymphoid neoplasms by height category

	Height*				
	1st quartile	2nd quartile	3rd quartile	4th quartile	5-cm increase
Lymphoid neoplasms					
Total					
Person-years	372,189	338,907	284,094	293,630	
No. of cases	113	82	68	82	
HR (95% CI)†	1.00 (reference)	0.96 (0.71-1.29)	0.99 (0.72-1.36)	1.38 (1.00-1.91)	1.15 (1.04-1.28)
Men					
Person-years	187,176	131,249	150,449	131,679	
No. of cases	64	45	40	48	
HR (95% CI)†	1.00 (reference)	1.15 (0.77-1.70)	1.00 (0.66-1.53)	1.72 (1.11-2.66)	1.24 (1.09-1.41)
Women					
Person-years	185,013	207,658	133,644	161,951	
No. of cases	49	37	28	34	
HR (95% CI)†	1.00 (reference)	0.76 (0.49-1.17)	0.97 (0.59-1.58)	1.05 (0.64-1.71)	1.03 (0.88-1.22)
ML					
Person-years	372,189	338,907	284,094	293,630	
No. of cases	88	60	47	62	
HR (95% CI)†	1.00 (reference)	0.91 (0.65-1.28)	0.88 (0.61-1.29)	1.37 (0.94-1.99)	1.14 (1.01-1.28)
PCM					
Person-years	372,189	338,907	284,094	293,630	
No. of cases	25	22	21	20	
HR (95% CI)†	1.00 (reference)	1.12 (0.62-2.02)	1.35 (0.73-2.50)	1.44 (0.74-2.80)	1.21 (0.99-1.47)
NHL					
Person-years	372,189	338,907	284,094	293,630	
No. of cases	55	47	41	45	
HR (95% CI)†	1.00 (reference)	1.08 (0.72-1.61)	1.12 (0.73-1.72)	1.42 (0.91-2.22)	1.14 (0.99-1.31)

*The ranges of each quartile for height were 115-160, 161-164, 165-168, and 169-199 cm for men, and 110-148, 149-152, 153-155, and 156-198 cm for women.

†HRs were adjusted for age at baseline (continuous), gender (men or women), study area (10 public health center areas), number of pack-years (0, 1-19, 20-29, 30-39, and ≥40 pack-years, as an ordinal variable), alcohol category at baseline (nondrinkers, occasional drinkers, and 1-149, 150-299, and ≥300 g/wk, as an ordinal variable), and weight category at baseline (four quartiles).

quartile for men and women were combined for the analysis of total subjects. For example, the 1st quartile of height for total subjects included the 1st quartile of height for men and for women. BMI was calculated from the self-reported height and weight by dividing the weight in kilograms by the square of height in meters. BMI was classified into five categories according to the guidelines for Asians issued by WHO Western Pacific region and others (26, 27), namely <18.5, 18.5-22.9, 23.0-24.9, 25-29.9, and ≥30 kg/m^2. Weekly ethanol intake was estimated by multiplying the amount of ethanol by the average frequency of drinking, as previously described (28). Subjects were classified into four categories on the basis of their drinking habits, namely nondrinkers and occasional drinkers (≤3 d/mo), and three categories of regular drinkers (1-149, 150-299, and ≥300 g/wk). With regard to smokers, the number of pack-years was defined as the product of the average number of packs smoked per day and the number of years the subject had been smoking, and used to classify the subjects into four categories (<5, 5-19, 20-39, and ≥40 pack-years).

Follow-up

Subjects were followed from the date of the baseline survey to December 31, 2006. Residence status and subject survival were confirmed annually through the resident registry in each area or, for those who had moved out of the study area, through the municipal office of the area to which they had moved. Among subjects, 7.5% changed residence and 0.5% were lost to follow-up during the study period. The incidence of cancer was determined by active patient notification from major local hospitals in the study area and by data collection from population-based cancer registries, with approval. ML and PCM were coded according

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to the criteria reported in the *International Classification of Diseases for Oncology*, 3rd edition. Information on cause of death was supplemented by checking death certificate files, with permission. Information was available from death certificates only in 6.4% of cancer cases. The earliest date of diagnosis was used for patients who developed multiple primary cancers at different times.

Statistical analysis

Person-years of follow-up for cancer incidence were accrued from the date of the baseline survey until the date of the occurrence of cancer, emigration from the study area, death, or the end of the study period, whichever came first. Subjects lost to follow-up were censored at the last confirmed date of presence in the study area. Study outcomes were defined as newly occurring ML or PCM during the study period. Adult T-cell leukemia/lymphoma was not included in the study outcome because it is a mature T-cell neoplasm caused by human T-cell leukemia virus type I (29), and evaluation of other risk factors in its development was difficult without information on baseline status of HTLV-I infection, which was not available in our survey. Hazard ratios (HR) and their 95% confidence intervals (95% CI) were calculated with the use of the Cox proportional hazards model to describe the relative risk of cancer associated with anthropometric characteristics. HRs were adjusted for the following potentially confounding factors: age at baseline (continuous), gender (men or women), study area (10 public health center areas), drinking habits (nondrinkers and occasional drinkers, regular drinkers of 1-149, 150-299, and ≥300 g/wk of alcohol), number of cigarette pack-years (0, 1-19, 20-29, 30-39 and ≥40), weight category (1st-4th quartile) in the analysis of height, and height category (1st-4th quartile) in the analysis of weight. We tested the assumption of proportional hazards by using the scaled Schoenfeld residuals and found no

Table 4. HRs and 95% CIs of lymphoid neoplasms by weight category

	Weight*				
	1st quartile	2nd quartile	3rd quartile	4th quartile	5-kg increase
Lymphoid neoplasms					
Total					
Person-years	344,960	325,700	313,243	304,917	
No. of cases	88	95	78	84	
HR (95% CI)†	1.00 (reference)	1.21 (0.90-1.63)	1.10 (0.80-1.51)	1.19 (0.85-1.66)	1.04 (0.97-1.11)
Men					
Person-years	160,290	164,901	132,722	142,642	
No. of cases	50	63	42	42	
HR (95% CI)†	1.00 (reference)	1.31 (0.90-1.92)	1.12 (0.72-1.74)	1.04 (0.66-1.66)	1.01 (0.92-1.10)
Women					
Person-years	184,670	160,799	180,521	162,276	
No. of cases	38	32	36	42	
HR (95% CI)†	1.00 (reference)	1.04 (0.65-1.68)	1.04 (0.65-1.66)	1.33 (0.83-2.14)	1.07 (0.96-1.19)
ML					
Person-years	344,960	325,700	313,243	304,917	
No. of cases	66	74	53	64	
HR (95% CI)†	1.00 (reference)	1.27 (0.90-1.78)	1.01 (0.69-1.47)	1.20 (0.82-1.76)	1.03 (0.95-1.11)
PCM					
Person-years	344,960	325,700	313,243	304,917	
No. of cases	22	21	25	20	
HR (95% CI)†	1.00 (reference)	1.05 (0.57-1.93)	1.35 (0.74-2.46)	1.14 (0.59-2.21)	1.06 (0.93-1.22)
NHL					
Person-years	344,960	325,700	313,243	304,917	
No. of cases	41	54	45	48	
HR (95% CI)†	1.00 (reference)	1.43 (0.95-2.16)	1.31 (0.84-2.04)	1.39 (0.88-2.19)	1.06 (0.97-1.17)

*The ranges of each quartile for weight were 30-57, 58-63, 64-69, and 70-115 kg for men, and 27-49, 50-53, 54-59, and 60-98 kg for women.

†HRs were adjusted for age at baseline (continuous), gender (men or women), study area (10 public health center areas), number of pack-years (0, 1-19, 20-29, 30-39, and ≥40 pack-years, as an ordinal variable), alcohol category at baseline (nondrinkers, occasional drinkers, and 1-149, 150-299, and ≥300 g/wk, as an ordinal variable), and height category at baseline (four quartiles).

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Table 5. HRs and 95% CIs of lymphoid neoplasms by BMI category

	BMI (kg/m^2)					
	<18.5	18.5-22.9	23.0-24.9	25.0-29.9	≥30.0	1-unit increase
Lymphoid neoplasms						
Total						
Person-years	37,898	549,106	336,345	330,909	34,563	
No. of cases	11	148	91	82	13	
HR (95% CI)*	1.02 (0.55-1.92)	1.02 (0.79-1.33)	1.00 (reference)	0.92 (0.68-1.24)	1.44 (0.81-2.59)	1.00 (0.97-1.04)
Men						
Person-years	15,026	250,578	167,153	155,547	12,251	
No. of cases	7	84	59	41	6	
HR (95% CI)*	1.14 (0.52-2.50)	0.93 (0.67-1.30)	1.00 (reference)	0.76 (0.51-1.14)	1.43 (0.62-3.33)	0.98 (0.93-1.03)
Women						
Person-years	22,872	298,529	169,191	175,362	22,312	
No. of cases	4	64	32	41	7	
HR (95% CI)*	0.90 (0.32-2.54)	1.19 (0.78-1.82)	1.00 (reference)	1.16 (0.73-1.84)	1.55 (0.68-3.51)	1.02 (0.97-1.07)
ML						
Person-years	37,898	549,106	336,345	330,909	34,563	
No. of cases	9	115	62	60	11	
HR (95% CI)*	1.25 (0.62-2.51)	1.18 (0.87-1.61)	1.00 (reference)	0.97 (0.68-1.39)	1.74 (0.91-3.32)	1.00 (0.96-1.04)
PCM						
Person-years	37,898	549,106	336,345	330,909	34,563	
No. of cases	2	33	29	22	2	
HR (95% CI)*	0.56 (0.13-2.36)	0.70 (0.42-1.15)	1.00 (reference)	0.79 (0.45-1.38)	0.76 (0.18-3.20)	1.01 (0.95-1.09)
NHL						
Person-years	37,898	549,106	336,345	330,909	34,563	
No. of cases	5	78	51	49	5	
HR (95% CI)*	0.84 (0.33-2.11)	0.97 (0.68-1.38)	1.00 (reference)	0.98 (0.66-1.45)	1.00 (0.40-2.52)	1.02 (0.97-1.07)

*HRs were adjusted for age at baseline (continuous), gender (men or women), study area (10 public health center areas), number of pack-years (0, 1-19, 20-29, 30-39, and ≥40 pack-years, as an ordinal variable), alcohol categories at baseline (nondrinkers, occasional drinkers, and 1-149, 150-299, and ≥300 g/wk, as an ordinal variable).

violation of proportionality. All statistical analyses were done with the use of the Stata version 11 software (Stata Corp.), with a *P*-value of <0.05 considered to be statistically significant.

Results

During 1,288,820 person-years of follow-up (average, 13.6 y) for 94,547 subjects (45,007 men and 49,540 women), a total of 257 cases of ML (152 men and 105 women) and 88 of PCM (45 men and 43 women) were newly diagnosed. By histologic subtype of ML, the distribution was diffuse large B-cell lymphoma in 80 (31.1%), follicular lymphoma in 18 (7.0%), marginal zone B-cell lymphoma in 16 (6.2%), precursor lymphoblastic leukemia/lymphoma in 11 (4.3%), Hodgkin lymphoma in 10 (3.9%), chronic lymphocytic leukemia/small lymphocytic lymphoma in 9 (3.5%), peripheral T-cell lymphoma of unspecified type in 5 (1.9%), other NHL in 13 (5.1%), NHL not otherwise specified in 53 (20.6%), and ML not otherwise specified in 42 (16.3%) subjects (Table 1).

Baseline characteristics of the study subjects are shown in Table 2. At baseline, younger subjects of both sexes were more likely to be taller and heavier, and younger men were more likely to have a higher BMI. Men who were heavy drinkers (≥300 g/wk of alcohol) were more likely to be in the 4th quartile of height and weight, and the BMI ≥30 kg/m^2 category. Current smokers of both sexes were more likely to be in the 4th quartile of height, whereas current male smokers were less likely to be in the 3rd or 4th quartile of weight or in the BMI ≥25 kg/m^2 category.

Compared with the 1st quartile, categorization in the 4th quartile for height showed a positive association with lymphoid neoplasm risk (HR, 1.38; 95% CI, 1.00-1.91), and an associated significant increase in lymphoid neoplasm risk was seen for each 5-cm height increase (Table 3). These associations were significant in men (HR 1.72; 95% CI, 1.11-2.66) but not in women (HR, 1.05; 95% CI, 0.64-1.71). However, no interaction was observed between height category and gender ($P_{interaction}$ = 0.466). A similar trend was observed for the subcategories of ML, PCM, and NHL, albeit the results were only

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marginally significant for PCM and NHL due to the small number of subjects in each category. In contrast, no association was observed between weight and lymphoid neoplasm risk (Table 4). We also found no significant association between BMI and lymphoid neoplasm risk, although high HRs were obtained for a BMI of ≥30 kg/m^2 compared with 23.0-24.9 kg/m^2 among men and women (Table 5).

Discussion

In this cohort study, we found that height was positively associated with risk of lymphoid neoplasms in a Japanese population. Compared with the lowest quartile of height, categorization in the highest quartile was significantly associated with a 38% increase in lymphoid neoplasm risk overall, and the association was significant among men. Similar trends were observed for the subcategories of ML, PCM, and NHL, albeit these were weak due to the small number of subjects in each category. On the other hand, we found no association between lymphoma neoplasm risk and weight or BMI. These findings suggest that early environmental exposure or genetic factors relating to height may affect the risk of lymphoid neoplasm.

A number of studies have evaluated the association between height and risk of lymphoid neoplasm. Several studies reported a positive association (5-9), whereas others reported no association (10-12). A cohort study done in 10 European countries (7) showed that the highest quartile of height was associated with a 50% increase in risk of NHL and PCM among women compared with the lowest quartile. In a cohort study in Korea (20), the highest quartile of height was associated with a 30% increase in risk of ML compared with the lowest quartile among men, with the trend being significant. In a case-control study in Japan (21), the highest quartile of height was associated with a 13% increase in risk of ML compared with the 2nd quartile; this finding was marginally significant, and the association was stronger among men. Consistent with these studies, we observed a 38% increase in risk of lymphoid neoplasms in the highest quartile compared with the lowest quartile among all subjects. This association was significant among men.

These consistent results across various ethnic populations suggest the presence of common mechanisms for the more frequent development of lymphoid neoplasms among taller than shorter people. One possibility is that various hormones affecting height in early life may be involved in cancer development. Height is thought to be determined by a combination of genetic factors and environmental exposures during infancy, childhood, and puberty (27). Intake of sufficient nutrients increases the level of various hormones, such as insulin-like growth factors (IGF) and growth hormones, which affect growth, sexual maturation, and probably many other processes relevant to cancer. Many studies confirmed that height is associated with several types of cancers, such as breast cancer (27), and important roles of IGFs and IGF-I receptors in development of cancer were shown by *in vitro* and *in vivo* studies (30). These have identified the role of bioavailable IGF-I in promoting cellular proliferation and inhibiting apoptosis through IGF-I receptor–mediated signaling mechanisms in various tissues, including hematopoietic cells (30). IGF-I affects the proliferation of various lymphoma cell lines in a dose-dependent manner (30), and the addition of an inhibitor that blocks the IGF-I receptor–mediated signaling pathway exerted antitumor activity against myeloma and lymphoma cells (31). Early exposure to IGF-I and other hormones may therefore affect the risk of lymphoid neoplasms. Another possibility is that cell division stimulated by IGF-I and pituitary-derived growth hormones may be higher in taller than shorter people (32). The risk therefore exists that more errors may be introduced in cells during DNA replication and that this may result in cancer (27).

The association between obesity and risk of lymphoid neoplasms is controversial. In a large pooled analysis of 18 case-control studies, obesity was not significantly associated with risk of NHL overall, but severe obesity (BMI ≥40 kg/m^2) was associated with risk of diffuse large B-cell lymphoma (14). Oh et al. reported that a BMI of 25.0 to 29.9 kg/m^2 was associated with a 54% increase in risk for NHL compared with a BMI of 18.5 to 22.9 kg/m^2, with marginal significance among Korean men (22), whereas Song et al. reported no association between BMI and ML risk among postmenopausal Korean women (23). In the present study, we observed no significant association between BMI at study entry and risk of lymphoid neoplasm, although point estimates of HR at a BMI ≥30 kg/m^2 were greater than unity with reference to a BMI of 23.0 to 24.9 kg/m^2 among men and women. However, our findings should be interpreted with caution because only 13 cases were detected in the obese category (BMI ≥30 kg/m^2). Clarification of this controversial issue will require evaluation of the association between BMI and lymphoid neoplasm risk among much larger Asian populations. Several recent studies showed that BMI at a younger age was more strongly associated with lymphoma risk than that at an older age (5, 6, 21). Maskarinec et al. (6) reported that body weight and BMI at age 21 years were stronger predictors of NHL risk than baseline anthropometric characteristics, suggesting that BMI during early adulthood may be a better indicator of NHL risk than weight at an older age. Their findings may support the significant association between height and lymphoma risk in the present study, on the basis that environmental exposure in early life affects not only height but also BMI during early adulthood, whereas BMI later in life may not represent the weight level during earlier years when body weight may have increased cancer risk through hormonal influences. Although insufficient information on the weight and BMI of subjects during early adulthood prevented us from fully evaluating the association between BMI in early adulthood and lymphoid neoplasm risk, evaluation of this possibility in a future cohort study would be worthwhile.

Several methodologic strengths of this study warrant mention. First, it was conducted as a prospective design with a high response rate (81%) and negligible proportion of losses during follow-up. The collection of information on anthropometric factors before the diagnosis of cancer excluded the exposure recall bias inherent to case-control studies. In addition, the study subjects consisted of general populations in various regions of Japan, and any geographical variation in confounding factors due to the diversity of study areas was adjusted for in the analysis.

The limitations of the study should also be mentioned. First, the statistical power in each stratified category may have been low due to the small number of cases in each category, and any findings for histologic subtypes should therefore be interpreted cautiously. Second, information on height and weight was obtained on the basis of a single self-report survey. However, the effect of misclassification would be minor, because the correlation between the self-reported values and measured values was considerably high (33).

In conclusion, we found that height was positively associated with risk of lymphoid neoplasm in a Japanese population, particularly among men. Because height may reflect early environmental exposure to various growth-related hormones, such as IGFs and growth hormones, or genetic factors relating to height, these factors may play an important role in the development of lymphoid neoplasm. Further studies are required to determine the mechanisms underlying these findings in our subject population.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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