Overweight and Obesity at Different Times in Life as Risk Factors for Non-Hodgkin's Lymphoma: The Multiethnic Cohort

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Abstract

Obesity may increase the risk for non-Hodgkin's lymphoma (NHL) through an inflammatory pathway. We explored the relation of NHL with body size at different times in life within the Multiethnic Cohort that includes African Americans, Caucasians, Japanese, Latinos, and Native Hawaiians. Participants were 45 to 75 years old at recruitment in 1993 to 1996. This analysis included 87,079 men and 105,972 women with 461 male and 378 female NHL cases. We used Cox regression to model NHL risk with age as the time metric while adjusting for age at baseline, ethnicity, education, alcohol intake, and age at first live birth. Body weight and body mass index at age 21 were stronger predictors of NHL risk than anthropometric characteristics at baseline. For men, being in the highest quartile of body mass index and body weight at age 21 conferred a nonsignificant 86% and 41% higher NHL risk, respectively, whereas there was no association at baseline. For women, the risk associated with the highest quartile of weight at age 21 was 1.6 (P_{trend} = 0.04), whereas women in the highest quartile at baseline had a nonsignificant risk of 27%. Height was positively related to NHL in men and women. Despite the small numbers, there was some consistency for risk estimates across ethnic groups and weak evidence for an association with NHL subtypes. These findings indicate that weight at age 21 may represent lifetime adiposity better than body weight at cohort entry. Alternatively, weight at age 21 may be more relevant for the etiology of NHL. (Cancer Epidemiol Biomarkers Prev 2008;17(1):196–203)

Introduction

Non-Hodgkin's lymphoma (NHL) has become the fifth most common cancer among men and women in the United States (1). The doubling of incidence since 1973 and the 50% higher risk for Caucasians than for African Americans, Japanese, Native Hawaiians, and Latinos are not well understood (2, 3). Adding complexity to the issue is the heterogeneity of the malignancy with at least 10 major subtypes (4). Immune dysfunction is thought to be the underlying basis of lymphoma development, but the well-known immunosuppressive states (that is, HIV infection and organ transplants) only partially explain the rising number of NHL cases. Also acting through an immune mechanism, overweight and obesity may be partially responsible for the growing risk. Elevated levels of tumor necrosis factor-α, interleukin-6, and leptin produced in adipose tissue (5-8) lead to a state of chronic inflammation (6, 9, 10) with an imbalance of cytokines that may stimulate the growth of B cells after initial transformation (11-13). A possible role of cytokines in the development of NHL is supported by significant associations between polymorphisms in the interleukin-10 and tumor necrosis factor-α gene and NHL risk (14, 15).

Epidemiologic evidence for an adverse effect of excess weight in relation to NHL was detected in several studies. A meta-analysis of 10 cohort studies and 6 case-control studies with 21,720 cases showed a risk estimate of 1.07 for overweight individuals, whereas obese persons were at a 20% higher risk for NHL (16). The aim of this study was to examine the importance of height, body mass index (BMI), and weight at different times in life within the Multiethnic Cohort (MEC), a prospective investigation in Hawaii and Los Angeles with Caucasians, Japanese, African Americans, Latinos, and Native Hawaiians. The diversity in ethnic groups within the MEC offers the opportunity to examine the effect of a wide range of body statures on NHL risk.

Materials and Methods

Study Population. The MEC was designed to provide prospective data on diet and other lifestyle exposures related to cancer risk. We sought to maximize the diversity of exposures, especially diet, by studying a variety of ethnic groups coming from all socioeconomic levels. Details on recruitment and baseline information have been published previously (17). The cohort was assembled in 1993 to 1996 by mailing a self-administered, 26-page questionnaire to persons who met the age and ethnicity criteria, identified primarily through the drivers' license files for the state of Hawaii and the county of Los Angeles in California, supplemented with other

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Table 1. NHL cases and subjects without NHL in the MEC Study

Characteristic	Women		Men	
	Cases (n = 378)*	Person-years at risk	Cases (n = 461)*	Person-years at risk
Age at cohort entry (y)				
45-54	57 (15.1)	189,839	67 (14.5)	115,880
55-64	121 (32.0)	325,541	136 (29.5)	207,288
65-74	183 (48.4)	333,271	227 (49.2)	330,883
≥75	17 (4.5)	111,781	31 (6.7)	110,418
Ethnicity				
Caucasian	110 (29.1)	231,107	133 (28.9)	195,651
African American	75 (19.8)	193,059	66 (14.3)	106,275
Native Hawaiian	23 (6.1)	69,072	27 (5.9)	52,624
Japanese	85 (22.5)	258,026	126 (27.3)	225,352
Latino	85 (22.5)	209,168	109 (23.6)	189,284
Education (y)				
≤12	192 (51.5)	433,975	188 (41.1)	308,876
13-16	138 (37.0)	400,073	213 (46.5)	346,781
>16	43 (11.5)	114,995	57 (12.5)	105,796
BMI at cohort entry (kg/m^2)				
<22.5	97 (26.4)	267,305	68 (14.9)	7,726
22.5-24.9	89 (24.3)	199,906	138 (30.2)	315,442
25-29.9	110 (30.0)	292,974	193 (42.2)	330,883
≥30	71 (19.4)	185,862	58 (12.7)	110,418
BMI at age 21 (kg/m^2)				
<18.5	49 (14.2)	171,304	37 (8.4)	52,688
18.5-24.9	267 (77.6)	647,738	338 (76.8)	573,707
25-29.9	22 (6.4)	50,993	54 (12.3)	92,898
≥30	6 (1.7)	16,684	11 (2.5)	13,616
Smoking				
Never smoker	214 (57.4)	525,187	125 (27.3)	230,958
Former smoker	113 (30.3)	281,904	255 (55.7)	392,648
Current smoker	46 (12.3)	135,892	78 (17.0)	137,225
Alcohol intake				
No alcohol	293 (77.5)	737,274	236 (51.2)	375,360
≤1 serving/d	54 (14.3)	140,015	97 (21.0)	174,477
>1 serving/d	31 (8.2)	83,143	128 (27.8)	219,349
NHL group				
DLBCL	132 (34.9)	—	152 (33.0)	—
Follicular	78 (20.6)	—	51 (11.1)	—
T cell	20 (5.3)	—	34 (7.4)	—
Small lymphocytic lymphoma/CLL	67 (17.7)	—	112 (24.3)	—
Other	81 (21.4)	—	112 (24.3)	—
Follow-up (y), mean	4.8	—	4.6	—

*Number of cases by category may add up to less than 461 due to missing values.

sources. Response rates varied from 20% in Latinos to 49% in Japanese Americans and yielded a highly representative group as evidenced by a comparison of the cohort distributions across educational levels and marital status with corresponding census data for the two geographic areas. The institutional review boards at the University of Hawaii and at the University of Southern California approved the study. The MEC includes 215,251 men and women ages 45 to 75 years at recruitment, primarily from five different racial/ethnic groups (African Americans, Japanese Americans, Latinos, Native Hawaiians, and Caucasians). We excluded 13,992 individuals because they did not belong to one of the five main ethnic groups, 8,264 subjects because their dietary information was deemed invalid, and 513 patients who were diagnosed with NHL/chronic lymphocytic leukemia (CLL) before entry into the cohort. Of the remaining 193,051 subjects, subjects with missing values for BMI at cohort entry (n = 2,541), BMI at age 21 (n = 12,849), height (n = 1,488), weight at cohort entry (n = 1,572), or weight at age 21 (n = 11,928) were not part of the respective analysis.

Identification of NHL Cases. Incident cancer cases within the MEC were identified by linkage with the Hawaii Tumor Registry and the Los Angeles County Cancer Surveillance Program using social security numbers. These National Cancer Institute–funded Surveillance, Epidemiology, and End Results registries ascertain all primary cancer diagnoses among residents of in their area. To cover a wider catchment area in California, we also did an annual linkage with the State of California Cancer Registry, also a Surveillance, Epidemiology, and End Results registry. Because we determined that after an average period of 7 years in the cohort the out-migration rate was only 3.7% (2.5% for California participants and 4.9% for Hawaii participants with California as the primary destination), we expect case ascertainment to be close to complete. From the linkages, we obtained the following information about each cancer patient: site, stage, histology, differentiation, grade, and disease-specific survival. Deaths in the cohort are identified by linkage to the state death certificate files in California and Hawaii and to the National Death Index for deaths occurring in other states. Case and death

Table 2. Anthropometric factors and NHL incidence by ethnic group

Variable	Men				
	Caucasian	African American	Native Hawaiian	Japanese	Latino
BMI at cohort entry (kg/m^2)	26.0 ± 4.0	26.7 ± 4.4	28.6 ± 5.4	24.7 ± 3.3	26.9 ± 4.0
BMI at age 21 (kg/m^2)	22.4 ± 3.0	22.4 ± 3.1	23.5 ± 4.0	21.7 ± 2.7	22.2 ± 3.6
Height (inches)	70.0 ± 2.9	70.0 ± 3.0	69.1 ± 2.8	66.1 ± 2.5	67.6 ± 2.9
Weight at cohort entry (pounds)	184.7 ± 31.9	189.7 ± 34.4	198.5 ± 42.1	156.7 ± 24.6	178.0 ± 29.5
Weight at age 21 (pounds)	159.2 ± 24.8	159.1 ± 24.8	163.1 ± 31.0	137.5 ± 19.8	146.8 ± 25.8
Annual weight change (pounds)	0.7 ± 0.8	0.7 ± 0.8	1.0 ± 1.1	0.5 ± 0.6	0.8 ± 0.8
NHL incidence*	21.0	19.0	16.2	14.1	18.1
DLBCL (%)	23.3	25.8	22.2	42.1	41.3
Follicular lymphoma (%)	9.8	6.1	14.8	13.5	11.9
T cell (%)	6.0	12.1	11.1	8.7	3.7
Small lymphocytic lymphoma/CLL (%)	39.9	31.8	18.5	9.5	19.3

NOTE: Mean ± SD unless otherwise noted.
*Per 100,000 persons; age adjusted to the 2,000 U.S. population truncated to ≥40 y.

ascertainment was complete until December 31, 2002. The following diagnoses by *International Classification of Disease for Oncology, Second Edition* histology codes were included in the study (4, 18): diffuse large B-cell lymphoma (DLBCL; 9675, 9680, and 9684), follicular lymphoma (9690, 9691, 9695, and 9698), T-cell lymphomas (9702, 9705, 9709, 9714, and 9718), small lymphocytic lymphoma (9670), CLL (9823), and other subtypes (9590, 9591, 9701, 9700, 9671, 9673, 9687, and 9699).

Study Variables. The baseline questionnaire collected information on demographics, medical and reproductive histories, body weight at cohort entry and at age 21, medication use, family history of various cancers, physical activity, and an extensive quantitative food frequency questionnaire. BMI was calculated as weight (kg) divided by height (m) squared. BMI at age 21 was categorized as <18.5 kg/m^2 (underweight), 18.5 to 24.9 kg/m^2 (reference), 25 to 29.9 kg/m^2 (overweight), and ≥30 kg/m^2 (obese) according to the WHO classification. However, only 1% of the study population was underweight (BMI <18.5 kg/m^2) at cohort entry, so we changed the cut point for the lowest category for BMI at cohort entry to 22.5 kg/m^2. Three indicator variables were created for height, weight at cohort entry, and weight at age 21 using quartiles based on the distribution in men and women separately. Annual weight change (pounds/y) was estimated by dividing the difference in weight at study entry and at age 21 by the number of years and categorized into as ≤1 pound/year, >1 pound/year, and no weight change or weight loss as the reference group.

Statistical Methods. All statistical analyses were done using the SAS Statistical Software version 9.1 (SAS Institute, Cary, NC). We calculated age-adjusted (2,000 U.S. population truncated to ≥40 years) incidence rates (per 100,000) by ethnicity for the time between cohort entry and the end of 2002. The risk of NHL due to different anthropometric factors (BMI and weight at cohort entry and at age 21, height, and weight change) was analyzed using Cox proportional hazards regression (PROC PHREG; ref. 19). We calculated hazard ratios (HR) and 95% confidence intervals (95% CI) using age as the time metric. The follow-up ended at the earliest of the following events: diagnosis of NHL, death, or December 31, 2002, the last date of follow-up. The models were stratified by follow-up time, categorized as ≤2, 2 to 5, and >5 years.

Because of previously reported associations, all models were adjusted for age at cohort entry, ethnicity, level of education, and alcohol intake (20). Age at first live birth was included as a covariate in the models among women because log-likelihood tests indicated a significant improvement of the models, whereas there was no evidence that smoking status, physical activity, hormone therapy, age at menarche, and age at and type of menopause improved model fit. Ordinal variables representing the median values for each quartile and the continuous BMI variable were used to test for linear trends. The proportional hazards assumption was tested by examining Kaplan-Meier survival curves and by assessing Schoenfeld residuals (19); no major violations were observed. The major analyses were done separately for men and women as there might be differences in NHL etiology. We estimated HRs for Caucasians, African Americans, Japanese, and Latinos and for DLBCL and follicular lymphoma. The number of cases for Native Hawaiians and the other NHL subgroups was too small for separate analyses.

Results

Between cohort entry and the end of 2002, 839 cases of NHL/CLL were diagnosed: 461 men and 378 women. Of these, 284 were DLBCL, 179 small lymphocytic lymphoma/CLL, and 129 follicular lymphoma (Table 1). The ethnic distribution of cases was 243 Caucasians, 141 African Americans, 211 Japanese, 194 Latinos, and 50 Native Hawaiians. At cohort entry, 36% of the 193,051 participants were diagnosed as being overweight, whereas 17% were obese. At age 21, 7% of subjects were classified as underweight, 14% as overweight, and 3% as obese. Of all subjects, 62% experienced an annual weight change of 1 pound or less, whereas 28% had an annual weight change of 1 pound or more. Native Hawaiian men had the highest mean BMI at cohort entry and at age 21 followed by Latinos and African Americans at cohort entry and by African American and Caucasian men at age 21 (Table 2). In women, African Americans reported the highest average BMI at cohort entry closely followed by Native Hawaiians and Latinos, whereas Native

Table 2. Anthropometric factors and NHL incidence by ethnic group (Cont'd)

Women				
Caucasian	African American	Native Hawaiian	Japanese	Latino
25.2 ± 5.5	28.6 ± 6.2	28.2 ± 6.6	23.1 ± 3.9	27.4 ± 5.4
20.6 ± 3.0	20.9 ± 3.7	21.8 ± 4.0	20.2 ± 2.6	21.4 ± 3.8
64.3 ± 2.7	64.5 ± 2.8	63.8 ± 2.6	61.2 ± 2.2	62.5 ± 2.7
151.2 ± 33.8	172.1 ± 38.4	166.4 ± 41.3	125.4 ± 22.3	154.7 ± 31.1
123.7 ± 19.4	126.1 ± 23.0	128.6 ± 25.6	109.3 ± 15.1	120.5 ± 21.2
0.7 ± 0.9	1.1 ± 1.0	1.1 ± 1.1	0.4 ± 0.5	0.8 ± 0.9
14.3	12.7	10.6	9.1	11.2
29.1	24.0	39.1	34.1	51.8
27.3	16.0	4.4	23.5	17.7
4.6	12.0	8.7	3.5	1.2
23.4	26.7	30.4	8.2	4.7

Hawaiians had the highest BMI at age 21 followed by Latinas and African Americans. The BMI was lowest for Japanese men and women at all times.

The respective male NHL incidence rates were highest for Caucasians, lowest for Japanese, and intermediate for African Americans, Latinos, and Native Hawaiians with lower rates in women than in men (Table 2). NHL types differed considerably by ethnicity. Japanese and Latinos had a higher proportion of DLBCL than Caucasians, African Americans, and Native Hawaiians, whereas the percentage of small lymphocytic lymphoma/CLL cases was highest in Caucasian and African American men. The proportions of follicular lymphoma and T-cell tumors were relatively similar by ethnicity.

BMI and body weight at age 21 were stronger predictors of NHL risk than at cohort entry in men

Table 3. NHL risk for anthropometric factors by ethnicity in men

Variable	All men (n = 461)		Caucasian (n = 133)		African American (n = 66)		Japanese (n = 126)		Latino (n = 109)	
	n*	HR (95% CI)	n*	HR (95% CI)	n*	HR (95% CI)	n*	HR (95% CI)	n*	HR (95% CI)
BMI at cohort entry (kg/m^2)										
<22.5	68	0.84 (0.63-1.13)	16	0.68 (0.39-1.21)	9	0.90 (0.41-1.99)	31	0.92 (0.58-1.45)	11	0.99 (0.49-1.99)
22.5-24.9	138	1.00	44	1.00	19	1.00	44	1.00	27	1.00
25.0-29.9	193	0.94 (0.75-1.18)	58	0.95 (0.64-1.41)	28	0.77 (0.43-1.38)	46	1.14 (0.75-1.73)	46	0.79 (0.49-1.28)
≥30.0	58	0.96 (0.70-1.32)	15	0.81 (0.44-1.49)	7	0.51 (0.21-1.22)	5	1.01 (0.40-2.57)	24	1.39 (0.80-2.43)
P_{trend}		0.61		0.66		0.18		0.40		0.53
BMI at age 21 (kg/m^2)										
<18.5	37	1.13 (0.81-1.59)	6	0.61 (0.27-1.40)	5	1.08 (0.43-2.72)	14	1.63 (0.93-2.85)	10	1.26 (0.65-2.45)
18.5-24.9	338	1.00	101	1.00	49	1.00	99	1.00	71	1.00
25.0-29.9	54	1.15 (0.86-1.54)	19	1.15 (0.70-1.91)	6	0.74 (0.32-1.74)	9	1.24 (0.62-2.46)	14	1.38 (0.78-2.46)
≥30.0	11	1.86 (1.02-3.40)	5	3.38 (1.37-8.36)	1	0.96 (0.13-6.96)	1	1.19 (0.16-8.55)	3	1.85 (0.58-5.89)
P_{trend}		0.27		0.02		0.55		0.45		0.42
Height (inches)										
<61.0	142	1.00	15	1.00	5	1.00	80	1.00	35	1.00
61.1-63.0	98	0.95 (0.73-1.25)	17	0.66 (0.32-1.35)	13	1.50 (0.53-4.20)	30	0.98 (0.64-1.50)	31	1.16 (0.71-1.89)
63.1-65.0	89	1.06 (0.79-1.42)	42	1.21 (0.66-2.22)	15	1.33 (0.48-3.67)	12	1.12 (0.61-2.06)	16	0.90 (0.49-1.64)
>65.0	129	1.39 (1.04-1.85)	59	1.18 (0.65-2.14)	30	1.69 (0.65-4.73)	4	1.18 (0.43-3.24)	27	2.05 (1.23-3.43)
P_{trend}		0.02		0.18		0.29		0.74		0.02
Weight at cohort entry (pounds)										
<152.0	118	1.00	15	1.00	8	1.00	73	1.00	19	1.00
152.0-170.0	108	0.90 (0.69-1.18)	28	1.03 (0.55-1.92)	18	1.18 (0.51-2.71)	30	0.79 (0.51-1.21)	28	0.98 (0.54-1.77)
170.1-192.0	128	1.09 (0.83-1.43)	52	1.50 (0.84-2.67)	23	1.10 (0.49-2.48)	18	1.04 (0.61-1.76)	27	0.92 (0.51-1.68)
>192.0	106	0.97 (0.72-1.31)	38	1.11 (0.61-2.03)	17	0.61 (0.26-1.41)	5	0.83 (0.33-2.09)	34	1.56 (0.88-2.78)
P_{trend}		0.92		0.70		0.07		0.65		0.08
Weight at age 21 (pounds)										
<130.0	110	1.00	11	1.00	4	1.00	70	1.00	21	1.00
130.0-145.0	107	1.16 (0.88-1.52)	26	1.47 (0.73-2.98)	19	2.77 (0.94-8.14)	29	0.88 (0.57-1.36)	25	1.23 (0.69-2.20)
145.1-165.0	124	1.25 (0.95-1.64)	43	1.55 (0.80-3.02)	24	2.16 (0.75-6.25)	17	0.92 (0.54-1.58)	33	1.79 (1.03-3.10)
>165.0	102	1.41 (1.05-1.91)	51	2.13 (1.10-4.12)	17	1.72 (0.58-5.13)	7	1.23 (0.56-2.73)	19	1.82 (0.97-3.41)
P_{trend}		0.03		0.02		0.80		0.90		0.02
Annual weight change (pounds)										
0 or loss	80	1.00	24	1.00	10	1.00	23	1.00	21	1.00
≤1	290	0.93 (0.72-1.19)	86	0.88 (0.55-1.39)	42	1.32 (0.66-2.64)	92	0.95 (0.60-1.51)	55	0.66 (0.40-1.11)
>1	91	0.86 (0.63-1.17)	23	0.67 (0.37-1.20)	14	0.93 (0.41-2.12)	11	0.96 (0.45-2.02)	33	0.84 (0.48-1.48)
P_{trend}		0.22		0.03		0.22		0.77		0.75

NOTE: Adjusted for age at cohort entry, ethnicity, education, and alcohol intake.
*May not add up to total due to missing values. Data for Native Hawaiians are not shown.

Table 4. NHL risk for anthropometric factors by ethnicity in women

Variable	All women (n = 378)		Caucasian (n = 110)		African American (n = 75)		Japanese (n = 85)		Latino (n = 85)	
	n*	HR (95% CI)	n*	HR (95% CI)	n*	HR (95% CI)	n*	HR (95% CI)	n*	HR (95% CI)
BMI at cohort entry (kg/m^2)										
<22.5	97	0.81 (0.61-1.10)	35	0.83 (0.50-1.39)	10	0.87 (0.40-1.93)	32	0.68 (0.39-1.15)	15	1.32 (0.63-2.77)
22.5-24.9	89	1.00	27	1.00	16	1.00	24	1.00	16	1.00
25.0-29.9	110	0.84 (0.63-1.12)	30	0.87 (0.51-1.47)	20	0.56 (0.29-1.08)	20	1.03 (0.57-1.88)	33	1.12 (0.59-2.10)
≥30.0	71	0.95 (0.69-1.32)	16	0.94 (0.50-1.75)	25	0.83 (0.44-1.56)	5	1.33 (0.50-3.54)	21	1.31 (0.66-2.59)
P_{trend}		0.60		0.79		0.60		0.06		0.88
BMI at age 21 (kg/m^2)										
<18.5	49	0.71 (0.52-0.96)	18	0.91 (0.54-1.54)	13	1.02 (0.54-1.90)	12	0.58 (0.31-1.08)	5	0.39 (0.16-0.97)
18.5-24.9	267	1.00	80	1.00	40	1.00	64	1.00	65	1.00
25.0-29.9	22	1.14 (0.73-1.78)	8	1.68 (0.81-3.51)	4	1.01 (0.36-2.84)	4	1.57 (0.57-4.34)	6	0.89 (0.36-2.21)
≥30.0	6	1.07 (0.47-2.41)	1	0.70 (0.10-5.05)	2	1.63 (0.39-6.78)	0	—	3	1.61 (0.50-5.14)
P_{trend}		0.03		0.44		0.75		0.08		0.06
Height (inches)										
<61.0	95	1.00	13	1.00	6	1.00	48	1.00	21	1.00
61.1-63.0	108	1.12 (0.84-1.50)	31	1.29 (0.66-2.51)	13	0.94 (0.36-2.47)	27	1.12 (0.69-1.80)	32	1.36 (0.77-2.41)
63.1-65.0	96	1.31 (0.95-1.79)	32	1.22 (0.63-2.39)	27	1.60 (0.66-3.88)	6	0.88 (0.37-2.07)	27	2.09 (1.16-3.74)
>65	73	1.24 (0.87-1.76)	33	1.18 (0.60-2.33)	28	1.67 (0.69-4.03)	1	0.63 (0.09-4.58)	5	0.95 (0.35-2.53)
P_{trend}		0.14		0.83		0.07		0.83		0.17
Weight at cohort entry (pounds)										
<125.0	85	1.00	26	1.00	5	1.00	37	1.00	11	1.00
125.0-143.0	106	1.48 (1.10-2.00)	27	0.91 (0.53-1.57)	13	1.31 (0.47-3.69)	33	2.17 (1.35-3.50)	27	1.70 (0.82-3.52)
143.1-167.0	83	0.97 (0.70-1.36)	31	0.90 (0.52-1.53)	15	0.75 (0.27-2.07)	10	1.34 (0.66-2.71)	22	0.93 (0.43-2.00)
>167.0	97	1.27 (0.91-1.79)	25	0.94 (0.54-1.65)	38	1.20 (0.47-3.07)	4	1.97 (0.69-5.62)	25	1.55 (0.74-3.24)
P_{trend}		0.53		0.86		0.62		0.05		0.55
Weight at age 21 (pounds)										
<105.0	61	1.00	13	1.00	6	1.00	31	1.00	11	1.00
105.0-118.0	112	1.59 (1.15-2.19)	36	1.39 (0.73-2.63)	15	1.54 (0.60-3.98)	29	1.46 (0.88-2.43)	24	1.52 (0.74-3.13)
118.1-127.0	78	1.28 (0.90-1.82)	25	0.94 (0.48-1.85)	11	1.02 (0.38-2.75)	16	1.58 (0.85-2.92)	21	1.59 (0.76-3.31)
>127.0	97	1.62 (1.15-2.29)	34	1.23 (0.65-2.34)	27	2.00 (0.82-4.87)	7	1.49 (0.65-3.40)	23	1.73 (0.83-3.60)
P_{trend}		0.04		0.87		0.10		0.16		0.19
Annual weight change (pounds)										
0 or loss	57	1.00	14	1.00	16	1.00	8	1.00	14	1.00
≤1	239	1.41 (1.05-1.90)	72	1.41 (0.78-2.56)	36	1.09 (0.59-2.00)	73	2.98 (1.43-6.20)	47	1.05 (0.56-1.95)
>1	82	1.05 (0.73-1.51)	24	1.27 (0.64-2.52)	23	0.67 (0.34-1.32)	4	1.59 (0.47-5.46)	24	1.00 (0.50-1.99)
P_{trend}		0.30		0.99		0.24		0.13		0.21

NOTE: Adjusted for age at cohort entry, ethnicity, education, alcohol intake, and age at first live birth.
*May not add up to total due to missing values. Data for Native Hawaiians are not shown.

(Table 3) and women (Table 4). Men in the highest categories of BMI and weight at age 21 had higher risks of NHL by 86% and 41% compared with the reference category, respectively (P_{trend} = 0.27 and 0.03), although based on small numbers in the highest category. For women, the risks associated with the highest BMI and weight at age 21 were 1.07 and 1.62 (P_{trend} = 0.03 and 0.04), respectively, also based on small numbers in the highest category. Women with a BMI below 18.5 kg/m^2 experienced a protective effect of 30% compared with normal BMI. Additional adjustment for height slightly decreased the effect of weight at age 21 on NHL (data not shown). Men in the highest quartile still showed an increased risk of NHL by 37% and women experienced a 54% higher risk, but these associations lost their statistical significance (data not shown).

In men and women, the risk of NHL by BMI and weight at cohort entry was close to one and showed no significant association with NHL. The trend tests for height were significant among men but not among women (P_{trend} = 0.02 and 0.14, respectively). The respective HRs for men and women in the highest quartile of height were 1.39 (95% CI, 1.04-1.85) and 1.24 (95% CI, 0.87-1.76). No significant trends were observed for men, but women with an annual weight change of 1 pound or less had a significant increased NHL risk compared with no weight change (HR, 1.41; 95% CI, 1.05-1.90).

Stratification by ethnicity showed similar HRs for BMI and weight at age 21 among Caucasian, Japanese, and Latino men, although the trend was only significant for Caucasians (P_{trend} = 0.02; Table 3). In African American men, no association between BMI at age 21 and risk of NHL was observed, but the HR for weight at age 21 was consistent with the other groups. Whereas Caucasian, Japanese, and Latino men showed no association between BMI at cohort entry and risk of NHL, a nonsignificant lower risk was observed in African Americans. Only in Latinos was there a suggestion of a higher risk with the highest quartile of weight at cohort entry. Although the risk associated with the highest height was elevated for all ethnic groups, the trend was only significant for Latino men (P_{trend} = 0.02). There was no association between weight change and NHL risk in men, except for Caucasians who had a lower risk associated with weight change (P_{trend} = 0.03).

Obesity at age 21 was nonsignificantly associated with NHL risk among African American and Latina women, whereas overweight at age 21 showed elevated HRs among Caucasian and Japanese women (Table 4). The higher NHL risk with a higher weight at age 21 was

consistent across all ethnic groups although not statistically significant. Whereas no association of BMI and weight at cohort entry with NHL was seen in Caucasian women, a nonsignificant higher risk was observed among African American, Japanese, and Latino women in the highest BMI and weight categories, with a borderline trend for BMI and weight at cohort entry (P_{trend} = 0.06 and 0.05, respectively) among Japanese women. The elevated risk associated with height was most pronounced in African American women (P_{trend} = 0.07), present to some degree in Caucasians and Latinas but not present in Japanese. Only Caucasian and Japanese women had a higher NHL risk with weight gain.

In men, we observed a nonsignificant 87% and 26% higher risk for DLBCL associated with weight at cohort entry and at age 21, respectively (Table 5). Little association was observed with BMI at either point in time. Follicular lymphoma showed an association with BMI at cohort entry that was close to significance (P = 0.09). Men in the highest categories of height, weight at cohort entry, weight at age 21, and annual weight change had elevated risks for follicular lymphoma. Women showed a nonsignificant increased risk of DLBCL by 45% for BMI at cohort entry, by 26% for height, and by 20% for weight at cohort entry but no association for the other variables (Table 6). Women who were obese at cohort entry experienced a 6-fold higher follicular lymphoma risk and weight change was also significantly related to follicular lymphoma (P = 0.04). However, the relation with height and weight was inverse.

Discussion

Consistent with the literature (21), overall NHL incidence was lower in all ethnic groups than in Caucasians: 10% lower for African Americans, 15% for Latinos, 25% for Native Hawaiians, and 30% for Japanese. BMI as well as weight during early adulthood were stronger predictors of NHL than these same characteristics measured at cohort entry. Subjects in the highest categories of BMI and weight at age 21 experienced an elevated NHL risk, whereas a protective effect of a BMI below 18.5 kg/m^2 was seen in women. We observed no overall association of BMI and weight at cohort entry in men and women. Height also increased NHL risk, but little association was observed with weight change. These results showed some consistency across ethnicities despite the very small numbers and the unstable risk estimates. BMI at cohort entry was associated with increased NHL risk among Latinos as well as among Japanese women. Obesity at age 21 conferred a higher NHL risk for Caucasians and Japanese as well as Latino men. In all ethnic groups, except Japanese women, a greater height was associated with a higher NHL risk. The risk estimates by subtype were unstable; more suggestive associations were observed for follicular lymphoma than for DLBCL.

Our findings disagree with a meta-analysis of 10 cohort and 6 case-control studies; it reported a 7% higher risk for overweight individuals and a 20% higher risk for obese persons (16). In contrast to our findings, the significant associations were restricted to DLBCL in the meta-analysis (16) and in a Scandinavian study (22). Looking at individual reports, evidence for an adverse effect of obesity in relation to NHL was detected in six case-control studies (5, 23-27), in two cohorts (28, 29), and for NHL mortality in two cohorts (30, 31), but in one of the studies this relation was limited to women (28). In the studies with significant findings, the estimated risks for a BMI of ≥30 kg/m^2 varied between 1.4 (27) and 3.1 (23). The only study in an Asian population found a similar risk as in Caucasians. NHL risk (unspecified subtypes) attributable to overweight in this Korean population was estimated as 6.2% (29). Four reports (5, 25-27) described an elevated risk for DLBCL and two of those also showed a higher follicular lymphoma risk for overweight individuals (5, 27).

On the other hand, NHL was not associated with BMI in six investigations (22, 32-36), but some of these were small and hospital-based. One reason for the discrepant findings may be that BMI does not represent percent body fat and body fat distribution very well. BMI has different validity as a measure for adiposity across ethnic groups; the use of population-specific cut points has been proposed (37-40). Despite their lower BMI, Asians tend to have a higher proportion of body fat (41) and are at risk

Table 5. Risk of DLBCL and follicular NHL for anthropometric factors in men

Variable	DLBCL (n = 152)		Follicular NHL (n = 51)	
	n*	HR (95% CI)	n*	HR (95% CI)
BMI at cohort entry (kg/m^2)				
<22.5	23	0.65 (0.35-1.21)	4	0.18 (0.03-1.07)
22.5-24.9	44	1.00	18	1.00
25.0-29.9	60	0.90 (0.56-1.43)	23	0.99 (0.30-3.23)
≥30.0	23	0.78 (0.40-1.52)	6	1.86 (0.44-7.86)
P_{trend}		0.69		0.09
BMI at age 21 (kg/m^2)				
<18.5	14	0.56 (0.27-1.15)	5	1.63 (0.35-7.72)
18.5-24.9	105	1.00	36	1.00
25.0-29.9	17	0.78 (0.41-1.48)	7	0.56 (0.10-3.05)
≥30.0	5	1.03 (0.36-2.91)	1	—
P_{trend}		0.51		0.51
Height (inches)				
<61.0	57	1.00	17	1.00
61.1-63.0	37	1.43 (0.84-2.42)	12	1.05 (0.27-4.09)
63.1-65.0	23	0.93 (0.48-1.80)	6	1.03 (0.14-7.69)
>65.0	34	1.32 (0.74-2.36)	16	3.89 (0.86-17.55)
P_{trend}		0.43		0.09
Weight at cohort entry (pounds)				
<152.0	47	1.00	14	1.00
152.0-170.0	37	1.97 (1.16-3.36)	11	1.92 (0.51-7.31)
170.1-192.0	32	1.36 (0.75-2.49)	13	0.99 (0.26-3.83)
>192.0	35	1.87 (0.95-3.68)	13	3.20 (0.74-13.84)
P_{trend}		0.12		0.18
Weight at age 21 (pounds)				
<130.0	43	1.00	16	1.00
130.0-145.0	34	0.87 (0.50-1.53)	10	0.97 (0.25-3.77)
145.1-165.0	38	1.24 (0.64-2.41)	8	3.58 (0.57-22.39)
>165.0	27	1.26 (0.63-2.50)	15	1.82 (0.39-8.37)
P_{trend}		0.33		0.47
Annual weight change (pounds)				
0 or loss	32	1.00	10	1.00
≤1	89	1.07 (0.62-1.86)	30	2.50 (0.48-13.07)
>1	31	1.14 (0.56-2.34)	11	5.34 (0.89-32.06)
P_{trend}		0.69		0.24

NOTE: Adjusted for age at cohort entry, ethnicity, education, and alcohol intake.
*May not add up to total due to missing values.

Table 6. Risk of DLBCL and follicular NHL for anthropometric factors in women

Variable	DLBCL (n = 132)		Follicular NHL (n = 78)	
	n*	HR (95% CI)	n*	HR (95% CI)
BMI at cohort entry (kg/m^2)				
<22.5	27	1.41 (0.66-3.00)	26	1.63 (0.67-3.98)
22.5-24.9	30	1.00	16	1.00
25.0-29.9	43	1.06 (0.58-1.96)	23	1.45 (0.62-3.41)
≥30.0	28	1.45 (0.75-2.82)	11	6.16 (1.75-21.71)
P_{trend}		0.80		0.20
BMI at age 21 (kg/m^2)				
<18.5	16	1.02 (0.50-2.10)	14	1.90 (0.72-4.99)
18.5-24.9	91	1.00	55	1.00
25.0-29.9	11	1.08 (0.50-2.33)	3	1.84 (0.26-12.83)
≥30.0	4	0.94 (0.25-3.55)	2	1.03 (0.16-6.84)
P_{trend}		1.00		0.47
Height (inches)				
<61.0	31	1.00	20	1.00
61.1-63.0	45	1.12 (0.62-2.04)	21	1.80 (0.54-6.02)
63.1-65.0	35	1.02 (0.52-1.99)	21	1.56 (0.42-5.84)
>65.0	19	1.26 (0.54-2.98)	15	0.31 (0.07-1.44)
P_{trend}		0.73		0.13
Weight at cohort entry (pounds)				
<125.0	26	1.00	21	1.00
125.0-143.0	38	0.74 (0.40-1.38)	21	0.35 (0.12-0.97)
143.1-167.0	35	1.35 (0.67-2.75)	17	0.40 (0.15-1.06)
>167.0	30	1.20 (0.57-2.52)	18	0.57 (0.18-1.75)
P_{trend}		0.40		0.54
Weight at age 21 (pounds)				
<105.0	22	1.00	18	1.00
105.0-118.0	34	0.70 (0.35-1.41)	29	0.80 (0.31-2.05)
118.1-127.0	34	0.97 (0.48-1.96)	13	0.32 (0.09-1.07)
>127.0	33	1.10 (0.53-2.29)	15	0.33 (0.11-1.01)
P_{trend}		0.44		0.03
Annual weight change (pounds)				
0 or loss	19	1.00	8	1.00
≤1	85	0.56 (0.21-1.55)	52	4.95 (0.38-65.27)
>1	28	0.93 (0.34-2.54)	18	7.75 (0.61-98.36)
P_{trend}		0.85		0.04

NOTE: Adjusted for age at cohort entry, ethnicity, education, alcohol intake, and age at first live birth.
*May not add up to total due to missing values.

for central adiposity (42). Because the adverse effect of excess body weight appears to be due to abdominal fat (43), waist circumference and waist/hip ratio may be better measures of adiposity than BMI (44). However, the Iowa women's cohort found no association between waist/hip ratio and NHL risk (34).

It is conceivable that weight early in life may be more relevant for NHL etiology than weight at an older age. In support of this idea, a British case-control study observed higher estimated risks associated with BMI for subjects diagnosed at younger ages (25). A large proportion of the cohort studies included in the meta-analysis recruited subjects at a younger age (16); the mean age was close to 40 years in several studies (29, 45, 46), whereas the mean age at entry into the MEC was 60 years. In the MEC, weight at age 21 may better represent lifetime weight status than weight at cohort entry because a large proportion of subjects may have undergone age-related weight changes due to disease, medication, or lifestyle by age 60.

This analysis had several limitations. Foremost, the relatively small number of cases, in particular by ethnic category and NHL subgroup, led to unstable estimates. The multiple comparisons for the subgroup analyses may have led to false-positive results. However, the MEC offers strength beyond the opportunity to perform analyses for individual ethnic groups. The most important advantage of a multiethnic population is the wide variation in exposure, such as BMI. Whereas the mean BMIs for Native Hawaiian men and women were above 28 kg/m^2, the respective values for Japanese were 24.7 and 23.1 kg/m^2 only (Table 2). We suspect that ethnicity is a confounder in the exposure/NHL relation; therefore, we controlled for it in our main models. Ethnicity may also be an effect modifier, but because of the relatively small number of NHL cases, we did not have adequate power to test statistically for effect modification by ethnicity.

As additional cancers occur in coming years, we will have more power to assess effect modification by ethnicity. Because many of the exposure/NHL relations have not been studied before in a multiethnic population, we present the effect estimates separately by ethnic group to see how effect estimates vary across ethnic groups. The prospective design and the information on self-reported weight at age 21 were considerable strengths of this study. Although remote weight recall is subject to certain biases, there is evidence that body weight earlier in life can be recalled with some accuracy as shown in elderly subjects (47), the Nurses' Health Study (48), a follow-up of U.S. adults (49), and the Newton Girls' Study (50). As discussed above, waist circumference would have been more informative to describe body fat levels than BMI because it is related to the amount of visceral fat (44).

As a possible mechanism, excess body fat may operate through an inflammatory pathway because adipose tissue produces cytokines (51), which are also B cell growth factors (52). The relation between adult height and NHL may be evident in men and not in women because cessation of vertical bone growth in women is correlated with age at menarche complicating the relation. Growth hormone is responsible for attainment of normal height and insulin-like growth factor-I is secreted in response to growth hormone. Both proteins are immunomodulators, affect thymic and B cell development, increase production of Th1 cytokines (IFN-γ) and tumor necrosis factor-α (in macrophages), and affect glucose metabolism and lipolysis as well (53). Thus, increased height may be related to NHL risk through an up-regulation of the growth hormone/insulin-like growth factor-I pathway.

In conclusion, these findings from the MEC support the hypothesis that adiposity, as assessed by height and body weight, may be risk factors for NHL. The results suggest that a higher BMI early in life may be more important in the etiology of NHL than overweight and obesity later in life. The age-specific incidence curve for NHL begins to rise slightly earlier than for other cancer sites, supporting the idea that early life exposures may be important (54).

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