

Body Mass Index, Physical Activity, and Risk of Multiple Myeloma

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Abstract

Several studies have reported a positive relation of baseline body mass index (BMI) with multiple myeloma, but data on other correlates of energy balance are limited. We undertook the present analyses to further examine the role of energy balance in multiple myeloma etiology in two large prospective cohorts with biennially updated exposure data. We followed members of the Nurses' Health Study and Health Professionals Follow-up Study cohorts from baseline until multiple myeloma diagnosis, death, or 2002. Adult height and current weight were reported at enrollment, and weight every 2 years thereafter. Physical activity was queried at baseline and updated every 2 to 4 years. We computed age-adjusted relative risks (RR) of multiple myeloma for categories of BMI and physical activity using Cox proportional hazards regression. We conducted analyses on each cohort separately and

on both cohorts combined. We confirmed 215 incident cases of multiple myeloma in the combined cohort of 136,623 individuals (>2.1 million person-years at risk). BMI was positively associated with multiple myeloma in all analyses. The association was strongest in men with a BMI of ≥ 30 kg/m² (versus a BMI of <22.0 kg/m²; RR, 2.4; 95% confidence interval, 1.0-6.0) and modest in overweight (BMI, 25-29.9 kg/m²) and obese (BMI, ≥ 30 kg/m²) women [versus BMI of <22.0 kg/m²; RR (95% confidence interval), 1.6 (1.0-2.7) and 1.2 (0.7-2.2), respectively]. Physical activity was not significantly related to multiple myeloma risk, although an inverse association was suggested in women. In conclusion, obesity seems to have an etiologic role in multiple myeloma, but the role of other correlates of energy balance remains uncertain. (Cancer Epidemiol Biomarkers Prev 2007;16(7):OF1-5)

Introduction

Multiple myeloma, a plasma cell neoplasm, is the second most common hematopoietic malignancy and accounts for ~1% of all cancers diagnosed in the United States (1). Close to 50,000 persons in the United States have multiple myeloma at the present time (1), and 19,900 new diagnoses are expected in 2007 (2). The incidence of multiple myeloma increases with advancing age and is higher among men and persons of African-American and Hispanic ethnicity (3, 4). Unfortunately, few risk factors other than age, sex, and race have consistently shown an association with multiple myeloma (5), hindering the development of prevention strategies. The identification of modifiable risk factors for this disease is particularly urgent because the 5-year survival rates remain below 40% (4) despite recent advances in targeted therapies. Of note, several large population-based studies have reported an increased risk of multiple myeloma with increasing body mass index (BMI; refs. 6-11). Those studies suggested that persons classified as "obese" by the common WHO definitions (i.e., BMI, ≥ 30 kg/m²; ref. 12) are approximately 1.5 to 2 times as likely as those with a "normal" BMI (<25 kg/m²) to develop multiple

myeloma. In one population of women (6), waist and hip circumference were also associated with modest increases in multiple myeloma risk.

Collectively, these data suggest that obesity or energy balance represents a potentially modifiable risk factor for multiple myeloma. However, it remains uncertain whether physical activity is also associated with this malignancy. In addition, the prior findings may be influenced by misclassification of BMI due to their reliance on a single (enrollment) assessment of adult weight (6-11). Thus, to further examine the relation of energy balance with multiple myeloma, we conducted prospective analyses of BMI and physical activity in the Nurses' Health Study and Health Professionals Follow-up Study cohorts. Data on both exposures are regularly updated among participants in these cohorts via biennial follow-up questionnaires. We therefore used Cox proportional hazards regression to assess whether current BMI measurements and an integrated measure of long-term average physical activity independently predict cancer risk. Under the assumption that a positive energy balance has an etiologic role in multiple myeloma, we hypothesized that current BMI would be positively associated with multiple myeloma, whereas physical activity would have an inverse relation.

Materials and Methods

Study Cohorts. The Nurses' Health Study was established in 1976 when 121,700 female registered nurses ages 30 to 55 years residing in 11 U.S. states returned an initial questionnaire (13). The Health Professionals Follow-up Study was initiated in 1986 among 51,529 U.S. male health professionals ages 40 to 75 years who completed the enrollment questionnaire. Follow-up questionnaires have been collected every 2 years from members of both cohorts to update information on lifestyle and disease history. The protocols for the studies were

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approved by the Human Subjects Research Committees at Brigham and Women's Hospital and at the Harvard School of Public Health, in accordance with assurances filed with and approved by the U.S. Department of Health and Human Services. Informed consent was implied by the participants' completion and return of the enrollment questionnaire.

Study Population. The 1980 questionnaire included the first queries on physical activity in the Nurses' Health Study. Thus, for analyses in this population, we defined the "baseline" cohort as women who responded to the 1980 questionnaire, had provided height data in 1976, and answered the physical activity and current weight questions in 1980. In the Health Professionals Follow-up Study, the baseline cohort comprised the men who provided information on adult height, weight, and physical activity at enrollment (i.e., in 1986). We excluded members of each cohort who had a history of cancer other than nonmelanoma skin cancer at baseline. The present analyses, therefore, included 89,663 women and 46,960 men, for a total of 136,623 persons in the combined analyses.

Exposure Assessment

Body Mass Index. Adult height and current weight were reported on the enrollment questionnaire in both cohorts, and current weight was updated on each subsequent (i.e., biennial) follow-up questionnaire. Self-reported height and weight were previously validated in these two cohorts and were found to be highly correlated with measured height and weight (14). We computed participants' current BMI at the start of each 2-year follow-up interval by dividing the current weight in kilograms by the square of the height in meters. When updated information on current weight was missing for a given follow-up interval, we carried forward the BMI calculated in the immediately prior interval, unless that interval also lacked the updated current weight information. In the latter case, we classified BMI as "missing." To assess the effect of excluding the intervals with missing updated BMI, we also conducted secondary analyses in which the BMI classification from more than one follow-up cycle before the interval with missing data was carried forward (i.e., so that no person-time or cases were omitted due to missing updated BMI information).

Physical Activity. In the Nurses' Health Study, women were asked in 1980 about the average number of hours they spent per week on a variety of activities such as vigorous sports, walking, cycling, jogging, and heavy gardening or housework. The 1982 questionnaire queried the average number of hours spent in activities that were strenuous enough to build up a sweat. In 1986, 1988, and from 1992 to 2000, nurses were asked to report the average number of hours spent per week during the prior year on specific activities such as walking or hiking (outdoors), jogging (>10 min/mile), running (≤ 10 min/mile), bicycling (outdoor or stationary), swimming, tennis or squash, aerobic dance, calisthenics, or use of a rowing machine. Because physical activity questions were not included in the 1984 and 1990 questionnaires, the cumulative average hours per week estimated as of the 1982 and 1988 questionnaires, respectively, were carried forward to characterize the person-time and new case diagnoses in the 1984 to 1986 and 1990 to 1992 follow-up intervals. In the Health Professionals Follow-up Study, each questionnaire from 1986 to 2000 included questions comparable with those asked of the Nurses' in the corresponding period (i.e., about the average hours per week spent on specific activities such as walking, jogging, running, bicycling, swimming, tennis/squash, rowing, and weight lifting). To characterize participants' long-term physical activity levels as precisely as possible (15), we integrated their responses to all the activity-related questions to calculate their cumulative average hours per week of moderate or strenuous physical activity

as of the start of a given follow-up interval. This physical activity metric was previously found to be informative for predicting all-cause and cancer-related mortality in the Nurses' Health Study population (15).

Identification of Cases. On the follow-up questionnaires, study participants in both cohorts reported new diagnoses of cancer that had occurred in the previous 2 years. Deaths among nonresponding cohort members were identified using the National Death Index, which was previously shown to be highly sensitive and specific in these cohorts (16, 17). For each self-report of a diagnosis of multiple myeloma, and for each potential case identified from a death certificate, we sought permission to obtain the medical records. A trained physician then reviewed the records to confirm the diagnosis according to established clinical criteria (18) and to confirm the date of diagnosis. The present analyses included all confirmed cases that were diagnosed from baseline through the cutoff date in 2002 (defined below).

Statistical Analyses. Accrual of person-time began on the date of return of the baseline questionnaire (i.e., 1980 for women and 1986 for men). We defined the study cutoff date as the date of mailing of the 2002 follow-up questionnaires: June 2002 for the women and January 2002 for the men. Baseline cohort members therefore contributed person-time until the earliest of three dates: diagnosis of cancer (other than nonmelanoma skin cancer), death, or January or June 2002. Follow-up intervals in which a participant's BMI data were missing were omitted from the main analyses. To maximize the information we could obtain about dose response from the continuous BMI data while also analyzing the common WHO classifications of 25 to <29.9 kg/m² (i.e., "overweight") and ≥ 30 kg/m² (i.e., obese; ref. 12), we used the baseline distribution of BMI in the Nurses' Health Study cohort to define two well-balanced categories among women with a BMI of <25 kg/m² (i.e., <22.0 kg/m² and 22 to <24.9 kg/m²). Thus, we analyzed a total of four BMI categories: <22.0 kg/m² (reference category), 22.0 to 24.9 kg/m², 25.0 to 29.9 kg/m², and ≥ 30 kg/m². We used the same BMI classification in the Health Professionals Follow-up Study to facilitate pooled analyses across the two cohorts. A BMI of <18.5 kg/m² (i.e., "underweight"; ref. 12) was infrequent in both cohorts. We also created four groups of cumulative average physical activity levels for consistency with those previously defined in the Nurses' Health Study population (15): <2.0 h/wk (reference category), 2 to 3.9 h/wk, 4 to 6.9 h/wk, and ≥ 7.0 h/wk. We calculated age in months at the start of each follow-up interval and modeled age as a continuous variable. To accommodate the time-varying exposure and covariate data, we used Cox proportional hazards regression models to calculate the relative risk (RR) of multiple myeloma for increasing category of biennially updated BMI and physical activity. We obtained 95% confidence intervals (95% CI) from the Cox models to characterize the precision of the point estimates. We conducted analyses within each cohort separately, as well as on the two study populations combined. To control for confounding due to age, we stratified each model by current age in months. When analyzing combined data from both cohorts, we also adjusted for study population, which achieved control for sex. We first constructed separate models with BMI or physical activity. We then evaluated BMI and physical activity concurrently as independent predictors. To obtain a *P* value for trend, we created continuous variables from the median values of the BMI or physical activity categories and entered those variables in additional age-stratified Cox models. All *P* values were two-tailed.

To explore whether weight loss due to preclinical disease affected the associations we observed between BMI and multiple myeloma in the main analyses, we conducted

Table 1. Distribution of risk factors for multiple myeloma by category of BMI at baseline in women (1980) and men (1986)

	BMI (kg/m ²)			
	<22.0	22.0-24.9	25.0-29.9	≥30.0
Women (N = 89,663)*	30,812	28,290	20,735	9,826
Men (N = 46,960) †	4,315	17,260	21,436	3,949
Mean				
Age, y (±SD)				
Women	45.3 (±7.2)	47.0 (±7.2)	48.2 (±7.0)	47.8 (±7.0)
Men	54.2 (±10.5)	54.1 (±10.0)	54.8 (±9.6)	54.3 (±9.0)
Physical activity (cumulative average hours/week) ‡				
Women	3.5	3.2	2.9	2.4
Men	3.5	3.6	3.2	2.5

*Nurses' Health Study cohort.

†Health Professionals Follow-up Study cohort.

‡Age-standardized within cohort.

additional analyses in which we classified multiple myeloma cases and person-time according to the BMI reported 4 or 8 years earlier. In those "lagged" analyses, we omitted the cases and person-time from the initial 4 or 8 years of follow-up.

Results

In the Nurses' Health Study, we identified 202 women with confirmed diagnoses of multiple myeloma in the 22 years of follow-up (>1.6 million person-years) from 1980 to June 2002. We excluded potential cases who reported a history of cancer other than nonmelanoma skin cancer at baseline (*n* = 3), did not return the 1980 questionnaire (*n* = 41), or did not complete the baseline physical activity questions (*n* = 15). Additional cases were excluded during follow-up due to the diagnosis of a different cancer (other than nonmelanoma skin cancer) before the multiple myeloma diagnosis (*n* = 16) or due to missing BMI data at the time of multiple myeloma diagnosis (*n* = 4). Some cases met more than one exclusion criterion; the final statistical models included 129 cases.

In the Health Professionals Follow-up Study, we identified 102 men with confirmed diagnoses of multiple myeloma during ~16 years of follow-up (>590,000 person-years) from enrollment through January 2002. From those, we excluded men with a missing date of birth (*n* = 2) or with missing baseline data on BMI (*n* = 2) or physical activity (*n* = 3). Additional cases were excluded during follow-up due to missing data on updated BMI (*n* = 11). Some cases met more than one exclusion criterion; the final analyses included 86 male cases.

At baseline, women in the higher BMI categories were slightly older, on average, than those in the lowest BMI category, whereas age did not vary by BMI in men (Table 1). Women and men in higher categories of BMI had lower average levels of physical activity at baseline.

We observed a positive relation of BMI with multiple myeloma (Table 2). In the Nurses' Health Study population, compared with women with a BMI of <22 kg/m² (i.e., the reference category), those with a BMI of 22 to 24.9 kg/m², 25 to 29.9 kg/m², and ≥30 kg/m² had age-adjusted and physical activity-adjusted RRs (95% CI) of 1.1 (0.7-2.0), 1.6 (1.0-2.7), and 1.2 (0.7-2.2), respectively. However, the *P* value for trend was not statistically significant. We observed a somewhat stronger association in the Health Professionals Follow-up Study cohort, especially among obese men (RR, 2.4; 95% CI, 1.0-6.0), and the trend was marginally significant (*P* = 0.07). In the combined analyses, we also observed a nonsignificant trend (*P* = 0.11) of increasing risk with increasing category of BMI after adjustment for age, physical activity, and study population. In those analyses, obese participants were 50% more likely to develop multiple myeloma than those with a BMI of <22 kg/m² (RR, 1.5; 95% CI, 0.9-2.5). Neither the 4-year lag nor the 8-year lag in classification of BMI had a notable effect on the results (data not shown). In addition, the results were not changed when we retained persons with missing updated BMI data in the analysis by carrying forward BMI information from more than one interval earlier (data not shown).

We did not observe a statistical relation of physical activity with multiple myeloma (Table 2). We did see a suggestion of an inverse association among women whose cumulative average hours per week of physical activity were higher than 2 (i.e., the reference category). The multivariable RRs (95% CIs)

Table 2. RR of multiple myeloma in men and women by category of BMI and physical activity level

	Cohort						
	Women*			Men †			Combined
	Cases (N = 129)	Person-years (N = 1,692,665)	RR (95% CI) ‡	Cases (N = 86)	Person-years (N = 590,631)	RR (95% CI) ‡	RR (95% CI) §
BMI (kg/m ²)							
<22	21	409,616	1.0 (reference)	7	50,291	1.0 (reference)	1.0 (reference)
22-24.9	32	494,927	1.1 (0.7-2.0)	32	200,193	1.3 (0.5-2.9)	1.2 (0.8-1.9)
25-29.9	53	502,613	1.6 (1.0-2.7)	31	276,679	1.0 (0.4-2.2)	1.3 (0.9-2.0)
≥30	23	285,499	1.2 (0.7-2.2)	16	63,469	2.4 (1.0-6.0)	1.5 (0.9-2.5)
<i>P</i> for trend			0.43			0.07	0.11
Physical activity (cumulative average hours/wk)							
<2	67	721,132	1.0 (reference)	25	154,734	1.0 (reference)	1.0 (reference)
2-3.9	30	530,295	0.6 (0.4-0.8)	17	143,714	0.7 (0.4-1.4)	0.6 (0.4-0.9)
4-6.9	28	359,299	0.9 (0.5-1.3)	19	142,990	0.8 (0.4-1.4)	0.8 (0.6-1.1)
≥7	4	81,930	0.5 (0.2-1.4)	25	150,193	0.8 (0.5-1.5)	0.7 (0.5-1.1)
<i>P</i> for trend			0.14			0.78	0.20
Cohort							
Women*							1.0 (reference)
Men †							1.3 (0.9-1.8)
<i>P</i>							0.12

*Nurses' Health Study cohort.

†Health Professionals Follow-up Study cohort.

‡From Cox proportional hazards models stratified by updated age (months) and mutually adjusted for BMI and physical activity.

§From Cox proportional hazards models stratified by age (months) and mutually adjusted for BMI, physical activity, and cohort.

||From age-stratified multivariable Cox models in which median BMI and physical activity category values were modeled as continuous variables.

for women reporting 2 to 3.9 h per week, 4 to 6.9 h per week, and ≥ 7 h per week of physical activity were 0.6 (0.4-0.8), 0.9 (0.5-1.3), and 0.5 (0.2-1.4), respectively (P for trend = 0.14). Among men, and in the combined analyses, increasing levels of physical activity were associated with only modest reductions in risk, and no trends were statistically significant.

In the combined cohort analyses, men (i.e., members of the Health Professionals Follow-up Study) were 30% more likely than women (i.e., Nurses' Health Study participants) to be diagnosed with multiple myeloma after adjustment for age, BMI, and physical activity (Table 2). Mutual adjustment for BMI and physical activity did not materially alter the associations that we observed in models that examined BMI or physical activity alone. For example, in women, the age-adjusted RRs (95% CI) for BMI were 1.3 (0.8-2.2), 1.7 (1.0-2.7), and 1.2 (0.7-2.2) for BMIs of 22 to 24.9 kg/m², 25 to 29.9 kg/m², and ≥ 30 kg/m², respectively, compared with the reference category of BMI of <22 kg/m² (P for trend = 0.45), without adjustment for physical activity. In men, the corresponding age-adjusted RRs (95% CI) were 1.3 (0.6-3.0), 1.0 (0.4-2.2), and 2.4 (1.0-6.0) for the same categories of BMI (P for trend = 0.09).

Discussion

We observed increasing risks of multiple myeloma with increasing BMI in two large prospective cohorts. Those findings were independent of physical activity, which was not significantly related to multiple myeloma risk. Current BMI showed a similar association with multiple myeloma as BMI characterized 4 to 8 years earlier. Thus, preclinical disease did not strongly influence the present findings. In previous reports, RRs of multiple myeloma ranged from 1.1 to 1.6 for a BMI of 25 to 29.9 kg/m² and from 1.4 to 2.2 for a BMI of ≥ 30 kg/m² (6-8, 10, 11). In addition, one study conducted in young Korean men reported a RR of 1.7 (95% CI, 1.1-2.7) for men with a BMI of 23 to 24.9 kg/m² (9). When reported separately for women and men, the BMI associations were somewhat stronger in men than in women (8, 10). The present findings are therefore consistent with the published literature. Of interest, the previous studies relied on a single (enrollment) classification of BMI (6-11). The similarity of the present report with those studies argues against an important effect of misclassification of BMI on the prior findings.

It is biologically plausible that obesity has a causal role in multiple myeloma. In particular, obese individuals have elevated levels of the proinflammatory cytokine interleukin-6 (IL-6; refs. 19-21). In fact, as much as 30% of total body IL-6 may be produced by adipocytes in obese individuals (20). IL-6 also has well-documented proliferative and antiapoptotic effects on multiple myeloma cells (22-24), and levels predict disease severity in patients with this malignancy (25, 26). Thus, IL-6 dysregulation is one plausible biological mechanism underlying the relation of BMI with multiple myeloma. Obesity is also associated with insulin resistance and other metabolic disorders that can result indirectly in the modulation of bioavailable insulin-like growth factor-I (27-29), another important growth and survival factor in multiple myeloma (30-32). Furthermore, synergy in the IL-6 and insulin-like growth factor-I pathways has been suggested by *in vitro* experiments on multiple myeloma cell lines (33). Thus, although BMI does not seem to correlate directly with circulating levels of insulin-like growth factor-I (29), obesity-related increases in bioavailable insulin-like growth factor-I may further contribute to multiple myeloma pathogenesis.

We did not observe a statistically significant association of physical activity with multiple myeloma in the present analyses, although a modest inverse association cannot be ruled out. Physical activity was not examined as an indepen-

dent risk factor in the previously published studies of obesity and multiple myeloma, but three of those studies reported baseline distributions of physical activity that did not differ notably by multiple myeloma status (6, 9, 10). To our knowledge, no other study has addressed the independent relation of physical activity with multiple myeloma. Thus, the collective evidence to date does not support an important independent etiologic role for physical activity.

A unique strength of the present study is the availability of prospectively acquired information on BMI and physical activity that was frequently updated during 16 to 22 years of follow-up. In addition, we used an integrated metric of long-term physical activity levels that would have minimized the effect of reverse causation due to limitations on activity by preclinical disease. The regression models were stratified finely by updated age in months and thus achieved precise control for confounding due to age. More than 90% of the members of both cohorts classified themselves as Caucasian, and therefore, there is little potential for confounding by race. Cigarette smoking is known to affect BMI, but smoking does not seem to be related to multiple myeloma (34-36), and therefore, we did not adjust for smoking in the present analyses. Although residual confounding is always a possibility, we are not aware of uncontrolled risk factors for multiple myeloma that are also correlates of BMI or physical activity and could explain the associations we observed. We assume that the modestly increased risk observed in the male Health Professionals cohort compared with the Nurses represents primarily a gender effect, consistent with descriptive epidemiologic reports indicating that Caucasian men have an ~50% higher incidence than Caucasian women (3, 4).

A potential limitation of the present analyses is our reliance on medical record review to confirm case diagnoses, without the reexamination of diagnostic specimens. However, despite the nonspecificity of several of the presenting symptoms (18), it is not evident that other conditions are frequently misdiagnosed as multiple myeloma (37, 38) or that delays in diagnosis are likely related to prospectively self-reported BMI or level of physical activity. We may have missed a few cases who did not respond to the follow-up questionnaire due to illness and are still alive or were too recently deceased to be identified through a National Death Index search. However, there is no evidence that nonresponse due to current health status is related to prospectively reported BMI or physical activity. Therefore, misclassification of disease seems unlikely to have biased the present findings.

Another potential limitation is the exclusion of cases due to missing baseline or updated exposure data. Among the Nurses' Health Study cohort, the proportion of excluded cases due to nonresponse to the 1980 (baseline) questionnaire is similar to the proportion of all cohort members who did not respond to the 1980 questionnaire, which was the first to include a food frequency questionnaire or questions on physical activity. Many of the omitted women did participate in subsequent follow-up questionnaires, and, as noted above, their nonresponse in 1980 is not likely to be related to their future risk of multiple myeloma. Among men, most of the case exclusions were due to missing updated BMI. Our secondary analyses that retained women and men with missing updated BMI in the analysis by reassigning BMI from earlier follow-up periods yielded results similar to those we have presented. Therefore, we do not believe that the exclusions due to missing exposure data have biased the present findings.

The predominance of Caucasians in the Nurses' Health Study and Health Professionals Follow-up Study cohorts may seem to limit the generalizability of our results; however, it is plausible that the biological mechanisms that underlie the observed relation of BMI with multiple myeloma function similarly in other ethnic groups. Consistent with this assumption, Brown et al. (7) observed elevated risks of multiple

myeloma with increasing BMI among both Caucasian and African-American participants in a population-based case-control study. Of interest, obesity was also more prevalent in the African-American control group in that study (7). Thus, as proposed by Benjamin et al. (39), a higher prevalence of obesity among African-Americans than in Caucasians might partially explain the well-documented racial differences in incidence of multiple myeloma in the United States (3, 4).

In conclusion, the present findings are consistent with previous reports of increasing risk of multiple myeloma with increasing BMI (6-11). This observation has been made across both cohort (6, 8, 9) and case-control (7, 10, 11) studies, and in Caucasian (6-8, 10), African-American (7), and Asian (9) populations, using a single baseline or frequently updated assessment of BMI. Although none of the studies can document the precise onset of preclinical disease in participants, the positive findings among prospective studies that include relatively long follow-up also argue for a temporal relationship of obesity preceding malignancy. Collectively, the data strongly suggest a causal role for obesity or a positive energy balance in the etiology of multiple myeloma. Additional research to elucidate the underlying biological mechanisms, including IL-6 and insulin-like growth factor-I dysregulation, as well as to examine other lifestyle correlates of BMI/energy balance as risk factors, such as weight change or weight cycling, will be valuable toward the translation of these findings to effective strategies to prevent this as yet incurable malignancy.

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