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Anthropometric, behavioral, and female reproductive factors and risk of multiple myeloma: a pooled analysis

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Abstract

Background—Risk of developing multiple myeloma (MM) rises with age and is greater among men and blacks than among women and whites, respectively, and possibly increased among obese persons. Other risk factors remain poorly understood. By pooling data from two complementary epidemiologic studies, we assessed whether obesity, smoking, or alcohol consumption alters MM risk and whether female reproductive history might explain the lower occurrence of MM in females than males.

Methods—The Los Angeles County MM Case-Control Study (1985-92) included 278 incident cases and 278 controls, matched on age, sex, race, and neighborhood of residence at case's diagnosis. We estimated MM risk using conditional logistic regression to calculate odds ratios (OR) and 95% confidence intervals (CI). In the prospective California Teachers Study (CTS), 152 women were diagnosed with incident MM between 1995-2009; we calculated hazard ratios using Cox proportional hazards analysis. Data from the two studies were pooled using a stratified, nested case-control sampling scheme (10:1 match) for the CTS; conditional logistic regression among 430 cases and 1,798 matched controls was conducted.

Results—Obesity and smoking were not associated with MM risk in the individual or combined studies. Alcohol consumption was associated with decreased MM risk among whites only (pooled OR=0.66, 95% CI=0.49-0.90) for ever vs. never drinking). Higher gravidity and parity were associated with increased MM risk, with pooled ORs of 1.38 (95% CI=1.01-1.90) for ≥3 versus 1-2 pregnancies and 1.50 (95% CI=1.09-2.06) for ≥3 versus 1-2 live births.

Conclusions—Female reproductive history may modestly alter MM risk, but appears unlikely to explain the sex disparity in incidence. Further investigation in consortial efforts is warranted.

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Keywords

multiple myeloma; women; reproductive; modifiable; risk factors; association; pooling; case-control; cohort; epidemiology

Introduction

Multiple myeloma (MM) accounts for nearly one-fifth of hematologic malignancies (1). MM incidence rises with age and is higher in African Americans, men, and among those with a family history of hematologic malignancies (1). Identification of sex-specific factors may offer clues to explain the male predominance in MM, but female reproductive history has also been inconsistently associated with MM risk in prior studies (2-4). Among lifestyle factors, some, but not all, evidence supports modestly elevated MM risk among obese persons (5, 6); results have been largely inconsistent for associations with smoking behavior and alcohol consumption (1). Most studies of MM have been case-control studies, which are susceptible to differential biases in exposure ascertainment and the loss of cases through early death or substantial illness that could affect interpretation of results.

To shed additional light on potential risk factors, we evaluated data from two complementary epidemiologic studies of MM conducted in California: a case-control study of men and women in Los Angeles (LA) County, and the longitudinal California Teachers Study (CTS) cohort of women only. We evaluated the associations of obesity, smoking, and alcohol consumption with MM risk, updating and expanding upon previous assessments of associations with anthropometry and alcohol consumption in the CTS (7, 8). We hypothesized that female steroid hormones may alter the immune response in a manner that decreases MM risk. The comparison of case-control and cohort-based analyses permitted us to evaluate consistency of associations and thus address potential biases in retrospective exposure ascertainment and participation (e.g., survival and selection bias) in case-control studies.

Materials and Methods

Study Populations

The Los Angeles County Multiple Myeloma Case-Control (LAMMCC) Study— The LAMMCC includes 278 cases (152 men, 126 women) diagnosed between 1985 and 1992 and 278 individually matched neighborhood controls from Los Angeles County. Incident MM cases were identified through rapid reporting in the Los Angeles County Cancer Surveillance Program, a population-based cancer registry; controls were recruited based on specific algorithms that placed their residence near the residence at diagnosis of their matched case, as previously reported (9). Controls were matched on date of birth within 5 years, sex, and race. All participants were interviewed in person. For evaluation of timing of exposures, a reference date was defined as the date of the case's diagnosis for both the case and matched control. When compared to Surveillance Epidemiology and End Results (SEER) data for the study period in LA County, the race distribution of cases was similar among men, but as per study protocol, blacks were oversampled among women. Age

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distributions compared to SEER were also equivalent, with the exception of the LAMMCC's exclusion of cases over 75 years. The study population was therefore largely representative of the general SEER population for LA County during the study period with the exception of study design attributes.

The CTS cohort—The CTS is a prospective cohort comprising 133,479 female public school professionals recruited through the California State Teachers Retirement System (10-12). In 1995-1996, participants completed a detailed, self-administered questionnaire that gathered information on demographics, anthropometric characteristics, lifestyle factors, and reproductive factors. Updates to menopausal status were obtained in follow-up questionnaires administered in 1997-98 and 2000-2001. For this analysis, we included 123,396 women after excluding those who, at baseline, had a previous diagnosis of MM or other hematologic cancers (n=536), had an unknown prior history of cancer (n=662), were not California residents (n= 8,867), or wished to participate only in breast cancer studies (n=18). Incident MM cases (ICD-O-3 9732-9733) were identified in the CTS through linkage with the California Cancer Registry. In the CTS, all cancers are identified prospectively by the Cancer Surveillance Program (>99% identification).

Follow-up time for each CTS participant began on the date the baseline questionnaire was completed and continued until the first of the following outcomes: a first diagnosis of any hematological malignancy, a move outside of California for >4 months, death, or the end of the follow-up period (December 31, 2009). The status of California residence was monitored through annual mailings, responses from participants and routine record linkages with multiple sources, including the US Postal Service National Change of Address database. The date and cause of death were ascertained through linkage with California and national mortality records (the Social Security Death Master File and the National Death Index).

Risk factors

We evaluated risk factors that were similarly queried in both studies. These characteristics included: cigarette smoking (never, current, or former; pack-years for current and former smokers), alcohol intake (number of glasses of beer, wine, and liquor consumed during a typical week prior to the reference date in the LAMMCC study and during the year prior to baseline in the CTS), body weight (pounds), height (inches), and corresponding body mass index (BMI) calculated as kg/m^2: (i) at age 18 years old and (ii) as an adult, defined as one year prior to MM diagnosis/reference date for the LAMMCC study and the participant's age at the date of the baseline questionnaire for CTS.

For analytic purposes, height, weight, and weight at 18 years old were evaluated as tertiles. The tertile values for the CTS were as follows for (a) height (inches): tertile 1 (<64), tertile 2 (64-65), tertile 3 (>65); (b) weight (pounds): tertile 1 (<131), tertile 2 (131-154), tertile 3 (>154); and (c) weight at 18 years (pounds): tertile 1 (<119), tertile 2 (119-130), tertile 3 (>130). The LAMMCC tertile values for females are as follows for (a) height (inches): tertile 1 (<62), tertile 2 (62-64), tertile 3 (>64); (b) weight (pounds): tertile 1 (<137), tertile 2 (137-164), tertile 3 (>164); and (c) weight at 18 years (pounds): tertile 1 (<111), tertile 2 (111-125), tertile 3 (>125). The LAMMCC tertile values for males are as follows for (a)

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height (inches): tertile 1 (<68), tertile 2 (68-70), tertile 3 (>70); (b) weight (pounds): tertile 1 (<168), tertile 2 (168-184), tertile 3 (>184); and (c) weight at 18 years (pounds): tertile 1 (<140), tertile 2 (140-160), tertile 3 (>160). Tertile values for pooled analyses (women only) are as follows for (a) height (inches): tertile 1 (<63), tertile 2 (63-65), tertile 3 (>65); (b) weight (pounds): tertile 1 (<131), tertile 2 (131-155), tertile 3 (>155); and (c) weight at 18 years (pounds): tertile 1 (<118), tertile 2 (118-129), tertile 3 (>129).

Female reproductive characteristics ascertained in both studies included number of pregnancies (combining live births, stillbirths, abortions, miscarriages, and ectopic pregnancies); number of live births; age at menarche; oral contraceptive use (years); and menopausal status (natural menopause, surgical menopause by bilateral oophorectomy or hysterectomy, premenopausal, or other/unknown). In the CTS, women under age 56 years who listed a simple hysterectomy as the cause of their last menstrual period were considered to have unknown menopausal status (13). In the LAMMCC study, menopausal status was ascertained at the referent date (date of diagnosis for the case) by asking if the women were still having menstrual periods. Those who indicated yes were identified as premenopausal, and those who indicated no were identified as menopausal. Surgical versus natural menopause was further delineated by their responses to whether they had a hysterectomy and/or an ovary removed before the referent date. In the CTS (but not the LAMMCC study), we were able to further discern between bilateral or unilateral oopherectomy with or without a hysterectomy.

Family history of hematologic malignancies was defined as having any first-degree relative with Hodgkin lymphoma, non-Hodgkin lymphoma, leukemia, or multiple myeloma (yes, no). Both studies ascertained family history of leukemia and other lymphomas, and the LAMMCC study also ascertained family history of multiple myeloma.

Statistical Analysis

To estimate relative risk for MM in the LAMMCC study, we used conditional logistic regression to compute odds ratios (ORs) and 95% confidence intervals (CIs) among men and women combined and by sex. In the CTS, we used multivariable Cox proportional hazards regression models to generate hazard rate ratios (HRs) and 95% CIs, with age in days from baseline until the end of follow-up as the time scale and models stratified by age in years at baseline and adjusted for race.

Both studies included additional multivariate adjustment for specific risk factors. BMI, smoking, and alcohol were adjusted for socioeconomic status (SES). Models for BMI and smoking were further adjusted for alcohol consumption. Numbers of pregnancies and live births were adjusted for age at menarche. SES in the LAMMCC study was based on education level (some high school or less; high school graduate; some college and above) because cases and controls were matched on neighborhood characteristics. The CTS data used residential neighborhood-level SES, based on address at baseline, as measured by a composite index that combined 1990 U.S. Census block-group-level data on education, income, and occupation, categorized into quartiles according to the California statewide distribution of the SES index (14). Different SES measures were used in the two studies because LAMMCC participants were matched on neighborhood, whereas nearly all CTS

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participants had at least a college degree. Additional adjustment for other risk factors, such as family history of hematopoietic malignancies, socioeconomic status, and further mutual adjustment for risk factors (e.g, BMI for reproductive factors, and vice versa) did not alter the risk estimates by ≥10%; we thus present the most parsimonious statistical models. Secondary analyses were conducted stratified by white or black race.

Pooled analysis—Cases and controls from the LAMMCC study were combined with a nested case-control sample of CTS participants. For each of the 152 MM cases in the CTS, we randomly selected 10 controls from risk sets matched on race, date of birth within 5 years, geographic region (San Francisco Bay Area, Southern California excluding Los Angeles, Los Angeles, Central/Southern California, Northern California excluding San Francisco, and the Central Valley). Our rationale for selecting 10 controls per MM case for the CTS was to maximize our power for detecting modest associations. Sensitivity analyses were also conducted whereby a 1:1 match was used to assure that our results were not weighted by the greater number of controls to CTS cases, compared to the LAMMCC study. The final pooled dataset thus comprised 430 cases and 1,798 controls.

We conducted conditional logistic regression to calculate ORs and 95% CIs for the pooled analyses. To retain matches, missing categories were created for each variable and covariates where applicable. The test for trend was obtained with logistic regression with each tertile coded as a 3-level ordinal variable for each tertile (0 = tertile 1, 1 = tertile 2, 2 = tertile 3). All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC).

Results

Table 1 shows selected demographic characteristics of participants by study, sex, and case status.

Anthropometric characteristics

Adult height was associated with increased MM risk among women but not men in the LAMMCC study (third versus first tertile OR=2.31, 95% CI=1.04-5.13), whereas the association was weaker among women in the CTS (HR=1.40, 95% CI=0.94-2.09) (Table 2). In the pooled analysis among women, MM risk remained marginally positively associated with elevated height (third versus first tertile OR=1.39, 95% CI=0.95-2.02) (Table 3). Adult and young-adult weight and BMI were not associated with MM risk in either study. Results stratified by race are shown in Supplemental Tables 1 and 2.

Cigarette smoking and alcohol intake

Smoking status was not associated with MM risk in either study (Table 2). Further evaluation by pack-years similarly yielded no associations with MM (data not shown).

Relative risk estimates for MM among ever versus never drinkers were all below 1.0 but not statistically significant in either the individual studies or in the pooled analysis. Evaluation of ever versus never alcohol consumption in the pooled analysis by race yielded a statistically significant decreased MM risk among whites (OR=0.66, 95% CI=0.49-0.90),

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but not among blacks (Supplemental Tables 1 and 2). We observed no specificity in risk by type of alcohol consumed (wine, beer, or liquor) and no evident dose-response association by number of drinks per day (data not shown).

Female reproductive characteristics

Compared with women with 1-2 pregnancies, women with 3 or more pregnancies had statistically significantly elevated MM risk in the CTS (HR=1.57, 95% CI=1.08-2.29); results for number of live births were similar (Table 2). In the LAMMCC study, the ORs were modestly above 1.0 and not statistically significant. In the pooled analysis, MM risk was statistically significantly associated with 3 or more versus 1-2 pregnancies (OR=1.38, 95% CI=1.01-1.90). Similarly, we observed a 1.50-fold increased MM risk (95% CI=1.09-2.06) among women with 3 or more versus 1-2 live births. The association was statistically significant among whites (OR=1.52, 95% CI=1.05-2.12), but not among blacks (Supplemental Tables 1 and 2). Surgical menopause was statistically significantly associated with increased MM risk in the LAMMCC study (OR=1.85, 95% CI=1.06-3.25), but not in the CTS (Table 2). In the pooled analysis, the OR remained above 1.0 but was of borderline statistical significance (OR=1.33, 95% CI=0.97-1.82) (Table 3). The positive association with surgical menopause was observed among whites, but not blacks (Supplemental Tables 1 and 2).

Discussion

This evaluation of anthropometric, behavioral, and reproductive risk factors revealed statistically significant increased risks of MM among women with higher gravidity or parity. Overall, we did not observe statistically significant associations for anthropometric features, alcohol consumption, or smoking behavior. Among whites only, we observed a statistically significantly modest decrease in MM risk with ever versus never alcohol consumption, but this was not accompanied by an inverse dose-response trend.

These null associations with anthropometric measures are consistent with findings from a nationwide Swedish cohort study and the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study (15, 16), but not U.S. cohort studies among men and women (Nurses' Health Study and Cancer Prevention Study cohorts) (17, 18). However, recent meta-analyses comprising a combined 8,982 incident multiple myeloma cases reported a modest 20% increase in MM risk among obese persons in both cohort (6) and case-control studies (5, 19). This positive association is further supported by recent evidence that risk for the precursor condition for MM, monoclonal gammopathy of undetermined significance, is elevated two-fold among obese persons (20). It is thus possible that our study lacked sufficient power to detect such a weak association.

The literature on smoking and MM risk remains unresolved, with one review article indicating no difference in MM risk with smoking (21), but more recent studies indicating some elevation in risk (1, 22). Our overall null association for smoking is consistent with results from other previous case-control and cohort studies (15, 23) and a recent meta-analysis of previously published case-control and cohort studies indicating no association (24). The evidence for alcohol consumption and MM risk is similarly unresolved, with

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results split between increased and decreased risks and an overall null association (1, 21). This is in contrast to the now relatively consistent protective association observed for non-Hodgkin lymphoma (25). Our findings add to the evidence that cessation of smoking is unlikely to influence MM risk, but further evaluation of associations with alcohol by race may be warranted.

We hypothesized that female steroid hormones may alter the immune response in a manner that decreases risk for MM. However, the positive associations of more pregnancies (resulting in fewer menstrual periods) and surgical menopause with MM risk may point to differences in hormone levels as a potential factor of interest for MM risk. Our results are consistent with findings from a recent case-control study of hematopoietic malignancies in Europe that also reported increased risk for women who reported being ever pregnant (3). However, we note that few studies have evaluated reproductive characteristics and of those who have, similar associations have not been reported (2). The modest positive association observed for increasing number of pregnancies may also suggest that repeated immunological changes, such as immune suppression that occurs during pregnancy (26, 27), promotes an environment that could contribute to MM development. Although we sought to identify reproductive characteristics that might explain the higher male to female ratio in MM incidence, our results suggest that higher female steroid hormones probably do not explain the lower MM incidence among female.

Differences in MM tumor characteristics by sex have previously been reported; female patients have more IgH translocations and inferior survival, whereas male patients have more frequent hyperdiploidy (28). Some epidemiologic associations have also varied by sex; for example, in the European Prospective Investigation on Cancer study, height was associated with increased MM risk among women but not men, and higher weight was associated with increased MM risk among men only (16). These differences could be due to chance, but biochemical studies have reported lower estrogen levels and a decreased estrogen-to-testosterone ratio among women with MM than women without MM (29, 30). These results point to potentially real biological differences in MM risk factors and tumor characteristics by sex.

The strengths of our analyses include our ability to compare results and pool from two complementary epidemiologic studies – a case-control study and a prospective cohort study conducted in the same geographic area – to identify consistent associations. Behavioral characteristics are particularly prone to recall bias in retrospective studies, and the parallel evaluation of the same characteristics in a prospective cohort is thus advantageous. Study limitations include the modest sample size for this rare cancer, limiting our ability to detect modest associations. Although our analysis included a sizable black population, stratified analyses by race were not robust due to small sample size. Thus, we cannot say with certainty if associations observed among whites (e.g., alcohol consumption) are definitely null among blacks. To increase validity, we limited our pooled analysis to variables that were asked in a consistent manner between the two studies. While differences in study design, exposure classification, and exposure prevalence, along with chance, may explain some of the lack of consistency in results between the two studies, they also make consistently observed associations particularly interesting. Consistency of associations

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between cohort data and case-control data was also beneficial due to potential biases among controls who participate. Specifically, as noted previously (31), selection bias among controls participants include higher education/SES and differences in reproductive factors, including lower birth order and parity than expected. These biases are known to result in muted risk estimates among case-control studies; while we cannot confirm whether ascertainment bias among controls occurred in the LAMMCC study, the lower risk estimate observed with the reproductive risk factors compared CTS would be consistent with this potential explanation.

In conclusion, our results suggest a possible role for female reproductive characteristics in MM etiology, albeit not in the direction that we hypothesized. We cannot discount the possibility that these findings are due to chance, but these consistent results from two complementary studies warrants further evaluation to confirm and better understand the roles of hormones and reproductive characteristics in MM development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Selected demographic characteristics of participants in the Los Angeles Multiple Myeloma case-control (LAMMCC) study (1985-1992) and the California Teachers Study (CTS) cohort (1995-2009).

	LAMMCC Study								CTS			
	Men				Women				Women			
Demographic characteristics	**MM cases (n=152)**		**Controls (n=152)**		**MM cases (n=126)**		**Controls (n=126)**		**MM cases (n=152)**		**Cohort (n=123,396)**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Race												
White	112	(74)	114	(75)	75	(60)	75	(60)	125	(82)	106,765	(87)
Black	21	(14)	21	(14)	39	(31)	39	(31)	12	(8)	3,288	(3)
Other/Unknown	19	(13)	17	(11)	12	(10)	12	(10)	15	(10)	13,343	(10)
Age at diagnosis (years)												
< 45	10	(7)			6	(5)			1	(1)		
45-54	22	(14)			22	(17)			11	(7)		
55-64	58	(38)			40	(32)			24	(16)		
65-74	60	(39)			58	(46)			45	(30)		
75+	2	(1)			0	(0)			71	(47)		
Family history of hematopoietic malignancies (first deg ree re lative s) [a]												
No	145	(97)	149	(98)	122	(98)	121	(98)	149	(98)	116,447	(97)
Yes	5	(3)	3	(2)	3	(2)	2	(2)	3	(2)	2,958	(3)
Education												
Some high school or less	26	(17)	26	(17)	26	(21)	34	(27)				
High school grad	28	(19)	32	(21)	47	(38)	37	(29)				
Some college and above	97	(64)	94	(52)	52	(42)	55	(44)				
Socioeconomic status (SES)												
Low									11	(7)	5,455	(4)
Med-Low									20	(13)	21,301	(17)

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	LAMMCC Study								CTS			
	Men				Women				Women			
Demographic characteristics	MM cases (n=152)		Controls (n=152)		MM cases (n=126)		Controls (n=126)		MM cases (n=152)		Cohort (n=123,396)	
	n	%	n	%	n	%	n	%	n	%	n	%
Med-High									57	(38)	39,935	(32)
High									63	(41)	55,123	(45)

[a] LAMMCC includes family history of multiple myeloma, leukemia, Hodgkin Disease or other lymphoma; CTS includes family history of leukemia, Hodgkin Disease or other lymphoma.

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Table 2

Evaluation of anthropometric, behavioral, and reproductive characteristics and multiple myeloma risk in the Los Angeles Multiple Myeloma case-control (LAMMCC) study and the California Teachers Study (CTS) cohort.

	LAMMCC Study										CTS			
	All[Δ]			Men[Δ]			Women[Δ]				Women 0			
	cases/controls	OR	95% CI	cases/controls	OR	95% CI	cases/controls	OR	95% CI	N	Person Years	Cases	HR	95% CI
Anthropometric characteristics														
Height at interview/Q1 (inches)														
Tertile 1	59/75	1.00	-	41/41	1.00	-	18/34	1.00	-	4048 3	501987	49	1.00	-
Tertile 2	119/98	**1.61**	**(1.01-2.55)**	59/49	1.24	(0.68-2.27)	60/49	**2.66**	**(1.23-5.77)**	3582 7	451149	47	1.29	(0.86-1.94)
Tertile 3	97/105	1.21	(0.77-1.90)	51/62	0.85	(0.48-1.50)	46/43	**2.31**	**(1.04-5.13)**	4650 5	589703	55	1.40	(0.94-2.09)
Weight at interview/Q1 (pounds)														
Tertile 1	91/91	1.00	-	44/50	1.00	-	47/41	1.00	-	4091 4	513633	52	1.00	-
Tertile 2	84/91	0.92	(0.62-1.38)	51/48	1.16	(0.68-1.99)	33/43	0.69	(0.37-1.26)	3791 0	479414	47	0.89	(0.60-1.32)
Tertile 3	99/96	1.02	(0.68-1.54)	55/54	1.15	(0.66-1.99)	44/42	0.89	(0.48-1.65)	3932 4	496648	46	0.83	(0.55-1.24)
BMI at interview/Q1* (kg/m2)														
<25	116/107	1.00	-	58/55	1.00	-	58/52	1.00	-	7207 9	909860	89	1.00	-

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	LAMMC C Study										CTS			
	All[Δ]			Men[Δ]			Women[Δ]				Women *0*			
	cases/ controls	OR	95% CI	cases/ controls	OR	95% CI	cases/ controls	OR	95% CI	N	Person Years	Cases	HR	95% CI
25-29.9	98/119	0.75	(0.51-1.10)	65/74	0.85	(0.52-1.39)	33/45	0.62	(0.34-1.17)	2945 9	370557	39	0.84	(0.57-1.23)
30-34.9	43/40	0.98	(0.59-1.62)	19/19	0.96	(0.46-2.01)	24/21	0.92	(0.45-1.88)	1072 3	135230	12	0.74	(0.40-1.36)
35+	21/12	1.86	(0.84-4.14)	8/4	1.80	(0.51-6.30)	11/8	1. 5 6	(0.55-4.40)	5843	73650	5	0.69	(0.28-1.72)
Weight at 18 (pounds)														
Tertile 1	85/92	1.00	-	44/50	1.00	-	41/43	1.00	-	4037 9	509068	49	1.00	-
Tertile 2	93/99	1.04	(0.67-1.60)	51/48	1.16	(0.68-1.99)	39/47	0.90	(0.48-1.69)	4069 3	513470	55	1.24	(0.84-1.84)
Tertile 3	92/83	1.22	(0.79-1.88)	55/54	1.15	(0.66-1.99)	42/34	1.33	(0.69-2.58)	3653 5	461122	42	1.17	(0.77-1.78)
BMI at 18*[a] (kg/m2)														
<20	80/87	1.00	-	31/33	1.00	-	49/54	1.00	-	3950 9	498005	54	1.00	-
20-21.9	84/82	1.07	(0.67-1.72)	45/40	1.21	(0.61-2.41)	39/42	0.92	(0.48-1.77)	3979 7	503198	41	0.75	(0.50-1.13)
22+	106/105	1.14	(0.72-1.79)	72/77	1.02	(0.55-1.87)	34/28	1.35	(0.67-2.73)	3766 1	474682	49	1.03	(0.70-1.51)
Smoking*[∞]														
Never	113/111	1.00	-	52/48	1.00	-	61/63	1 . 0 0	-	8119 7	102768 8	92	1.00	-

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	LAMMC C Study										CTS			
	All[Δ]			Men[Δ]			Women[Δ]				Women 0			
	cases/controls	OR	95% CI	cases/controls	OR	95% CI	cases/controls	OR	95% CI	N	Person Years	Cases	HR	95% CI
Ever	165/167	1.01	(0.71-1.43)	100/104	0.88	(0.54-1.46)	65/63	1.10	(0.67-1.80)	41 42 7	511790	58	1.10	(0.78-1.54)
Current	40/54	0.79	(0.48-1.32)	25/32	0.72	(0.35-1.48)	15/22	0.73	(0.35-1.54)	35201	437341	47	1.50	(0.80-2.83)
Former	125/113	1.09	(0.75-1.59)	75/72	0.93	(0.55-1.56)	50/41	1.31	(0.75-2.29)	6226	74449	11	1.03	(0.72-1.448)
Alcohol*														
Ever	130/121	1.00	-	54/46	1.00	-	76/75	1.00	-	3910 2	483209	56	1.00	-
Never	148/156	0.86	(0.59-1.24)	98/105	0.81	(0.49-1.34)	50/51	0.93	(0.54-1.60)	7657 9	972509	82	0.81	(0.57-1.15)
Female reproductive characteristics														
Number of pregnancie◇														
0							8/12	0.64	(0.22-1.84)	2508 9	312069	24	1.27	(0.77-2.09)
1-2							41/41	1.00	-	4963 1	624835	43	1.00	-
3+							77/73	1.11	(0.64-1.93)	4619 8	582521	79	**1.57**	**(1.08-2.29)**
Number of live births◇														
0		N/A			N/A		15/17	0.96	(0.43-2.16)	3267 2	407453	31	1.23	(0.79-1.91)

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	LAMMC C Study										CTS			
	All[Δ]			Men[Δ]			Women[Δ]				Women[0]			
	cases/ controls	OR	95% CI	cases/ controls	OR	95% CI	cases/ controls	OR	95% CI	N	Person Years	Cases	HR	95% CI
1-2							48/53	1.00	-	5919 8	749179	54	1.00	-
3+							63/56	1.29	(0.76 - 2.18)	2910 0	363453	61	**1.58**	**(1.09 - 2.31)**
Menopausal status														
Natural menopause							47/61	1.00	-	4792 8	633322	15	1.00	-
Surgical menopause (hysterectomy or oopherectomy)							67/48	**1.85**	**(1-06 - 3.25)**	3905 9	469463	72	1.12	(0.76 - 1.64)
Premenopausal							11/16	0.64	(0.19 - 2.19)	2017 7	242422	42	0.80	(0.33 - 1.94)

[Δ]LA MM case-control study estimates matched on sex, date of birth +/− 5 years, and race

[0]CTS estimates adjusted for age and race *Additional adjustments for individual models include*: **SES (CTS) or education (case–control)*

[∞]alcohol

[◇]age at menarche

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Table 3

Multiple myeloma risk for select anthropometric, behavioral, and reproductive characteristics from pooled analyses of the Los Angeles Multiple Myeloma case–control (LAMMCC) study and the California Teachers Study (CTS) cohort with matched controls (10:1).

	All[Δ]			Women[Δ]			
	cases/controls	**OR**	**95% CI**	**cases/controls**	**OR**	**95% CI**	**P-heterogeneity**
Anthropometric characteristics							
Height at interview/Q1 (inches)							
Tertile 1	115/482	1.00	-	74/441	1.00	-	
Tertile 2	174/734	1.20	(0.89-1.62)	115/685	1.21	(0.85-1.72)	
Tertile 3	137/569	1.18	(0.86-1.61)	86/507	1.39	(0.95-2.02)	
	p-trend=0.33			*p-trend=0.10*			0.52
Weight at interview/baseline (pounds)							
Tertile 1	133/560	1.00	-	89/510	1.00		
Tertile 2	134/563	0.95	(0.71-1.28)	83/515	0.87	(0.61-1.23)	
Tertile 3	152/573	0.95	(0.71-1.27)	97/519	0.88	(0.62-1.24)	
	p-trend=0.65			*p-trend=0.34*			0.93
BMI at interview/baseline* (kg/m2)							
<25	205/906	1.00	-	147/851	1.00	-	
25-29.9	137/526	0.79	(0.60-1.04)	72/452	0.79	(0.57-1.11)	
30-34.9	55/195	0.85	(0.58-1.24)	36/176	0.83	(0.53-1.30)	
35+	22/69	1.05	(0.59-1.88)	14/65	0.91	(0.46-1.80)	
	p-trend=0.49			*p-trend=0.38*			0.63
Weight at 18 years (pounds)							

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	All[Δ]			Women[Δ]			
	cases/controls	OR	95% CI	cases/controls	OR	95% CI	P-heterogeneity
Tertile 1	140/552	1.00	-	96/503	1.00		
Tertile 2	138/555	1.15	(0.85-1.56)	84/503	1.14	(0.80-1.63)	
Tertile 3	138/578	1.17	(0.86-1.59)	88/529	1.18	(0.83-1.70)	
	p-trend=0.30			*p-trend=0.33*			0.28
BMI at 18[*] (kg/m2)							
<20	134/553	1.00	-	103/520	1.00		
20-21.9	125/580	0.87	(0.64-1.19)	80/540	0.78	(0.54-1.11)	
22+	155/539	1.02	(0.75-1.39)	83/462	1.07	(0.75-1.53)	0.29
Smoking[*∞]							
Never	205/1073	1.00	-	153/1025	1.00		
Ever	223/719	1.07	(0.84-1.37)	123/615	1.09	(0.83-1.44)	0.15
Current	51/117	0.97	(0.64-1.47)	26/85	1.11	(0.67-1.87)	
Former	172/602	1.10	(0.84-1.42)	97/530	1.09	(0.81-1.46)	
Alcohol[*]							
Never	186/628	1.00	-	132/582	1.00	-	
Ever	230/1142	0.79	(0.61-1.02)	132/1037	0.78	(0.58-1.06)	0.74
Female reproductive characteristics							
Number of pregnancies[◇]							
0				32/268	1.04	(0.66-1.66)	

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	All[Δ]			Women[Δ]			
	cases/controls	OR	95% CI	cases/controls	OR	95% CI	P-heterogeneity
1-2				84/602	1.00	-	
3+				156/736	**1.38**	**(1.01-1.90)**	0.35
Number of live births[◇]							
0				46/334	1.14	(0.77-1.70)	
1-2		N/A		102/739	1.00	-	
3+				124/534	**1.50**	**(1.09-2.06)**	0.61
Menopausal status							
Natural menopause				119/808	1.00		0.01
Surgical menopause (hysterectomy or oopherectomy)				109/438	1.33	(0.97-1.83)	
Premenopausal				26/210	0.60	(0.30-1.21)	
Other/unknown				24/190	1.25	(0.75-2.07)	

[Δ]Matched on sex, date of birth +/− 5 years, and race *Additional adjustments for individual models include:*

[*]education level

[◇]age at menarche

[∞]Malcohol