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Medication use and multiple myeloma risk in Los Angeles County

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Abstract

Background—The role of medication use in multiple myeloma (MM) risk remains unclear.

Methods—The Los Angeles County Multiple Myeloma Case-Control Study, comprising 278 MM cases and individually-matched neighborhood controls, provided data to assess associations between medication use and MM risk. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using conditional logistic regression.

Results—Erythromycin (ever) use was associated with increased MM risk (OR=1.85, 95% CI=1.13–3.03). This association was restricted to men (OR=3.77, 95% CI=1.72–8.29) and was especially apparent among men who took two or more courses of erythromycin (OR=4.68, 95% CI = 1.70– 12.87).

Conclusions—Compared to females, males have lower levels of CYP3A4, for which erythromycin is both a substrate and inhibitor. Use of CYP3A4-inhibiting drugs such as erythromycin in men may thus result in even lower levels of CYP3A4 and, consequently, higher levels of CYP3A4-metabolized substances. These results could potentially provide clues to explain discrepancies in MM incidence by sex. Consortial efforts to confirm these associations are warranted.

INTRODUCTION

Multiple myeloma (MM) arises from malignant plasma cells derived from post-germinal center B-cells [1]. An estimated 24,050 new MM cases will be diagnosed in the United States in 2014 [2]. Established MM risk factors in decreasing order of magnitude of risk are higher age, black race, family history of MM, and being male [3]. We continue to search for additional risk factors and to understand the underlying mechanisms explaining the higher MM risks among men and blacks.

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Risk factors altering the host immune response, such as medication use, are hypothesized to influence MM risk [4]. However, evidence supporting the role of medication use in MM risk remains scant [5] though a handful of studies do suggest a potentially elevated MM risk in individuals who report having taken specific medications, such as erythromycin [6], laxatives [7], and some corticosteroids [4, 8]. Because results have been inconsistent [7] and limited by small numbers of cases within the reported studies (range: 14–179 cases) [4, 6] we analyzed data on medication use collected from participants in the Los Angeles County Multiple Myeloma Case-Control Study (LAMMCC).

MATERIALS AND METHODS

Methods in the LAMMCC have been described in detail previously [9]. Briefly, the LAMMCC recruited 278 MM (152 male/126 female; 189 white/60 black) patients living in Los Angeles County, California, newly diagnosed from 1985–1992, identified through the Los Angeles County Cancer Surveillance Program. One neighborhood control (living in proximity to the case's residence at the time of diagnosis) was recruited and individually matched to each case on sex, race, and date of birth within five years. Participants were interviewed in person between 1985 and 1992 regarding a wide range of possible risk factors. A reference date (the patient's diagnosis date) was assigned to each case-control pair and medication use was queried prior to that date. Selected demographic characteristics are shown in Table 1.

The following medications queried in the LAMMCC questionnaire were evaluated for MM risk: amphetamines, antibiotics (erythromycin, penicillin or ampicillin, and tetracycline), non-insulin antidiabetics, benzodiazepines, gout medication, non-steroidal anti-inflammatory drugs (indometacin and all other NSAIDs), phenytoin, steroids, and sulfonamides (Table 2). Other medications (such as statins or aspirin) were not evaluated as they were not queried in the LAMMCC questionnaire. For medication use, any use and, where pertinent, number of treatment courses, was ascertained. Odds ratios (ORs) and 95% confidence intervals (CIs) for MM risk for ever use compared to never use were estimated using conditional logistic regression. Where pertinent, *p*-trend was computed using the Cochran-Armitage test for trend. Adjustment for family history of hematopoietic malignancies did not alter risk estimates (<10%) and was thus not included in the final models. A number of infections were assessed, including the most recent visit to a healthcare provider, for urinary tract or bladder infections, eye infections, respiratory infections, bronchitis, sinusitis, and strep throat or tonsillitis. Participants reporting having seen a doctor or sought medical care for any of those infections (for which erythromycin might have been indicated) in the five years prior to MM diagnosis (or reference date for controls) were excluded in sensitivity analysis to minimize protopathic bias. Analyses were conducted using SAS 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Among all participants, ever use of erythromycin was statistically significantly associated with elevated MM risk (OR=1.85, 95% CI=1.13–3.03), particularly with at least two or more courses of treatment (Table 2). This association was observed among men (Men:

OR=3.77, 95% CI=1.72–8.29; Women: OR=1.00, 95% CI=0.51–1.98) (Supplemental Table 1). Among men taking two or more courses of erythromycin, the effect is further pronounced (OR=4.68, 95% CI=1.70–12.87) (Supplemental Table 1). In sensitivity analyses, exclusion of participants who reported having a bacterial infection five years prior to their MM diagnosis (or referent date) did not alter the magnitude of the risk between erythromycin use and MM risk.

Two other medications evaluated for MM risk previously [4, 7] produced elevated but not statistically significant associations with MM risk in the LAMMCC (ever use of phenytoin: OR=2.71, 95% CI=0.71–10.34; gout medication: OR=1.38, 95% CI=0.68–2.82). We did observe a statistically significant increased MM risk associated with ever use of sulfonamides (OR=1.65, 95% CI=1.02–2.68) (Table 1), particularly among blacks (OR=4.84, 95% CI=1.28–18.26) (Supplemental Table 2).

DISCUSSION

Use of erythromycin, a commonly prescribed macrolide antibiotic, was associated with a nearly twofold increased risk of MM, primarily among men, in the LAMMCC study. Although this is the first such report in a population-based case-control study, these results support the first reported link between erythromycin use with MM (SMR=2.7) based on an analysis of pharmacy records of 13,941 individuals using erythromycin from 1969–73 and followed through 1980 in the Kaiser Permanente Medical Care Program [6].

Erythromycin is both a substrate for [10] and potent inhibitor of [11] the hepatic enzyme cytochrome P450 3A4 (CYP3A4). CYP3A4 is responsible for the clearance of a variety of xenobiotics [12], including erythromycin. CYP3A4 expression levels vary across the population [13] and are known to be lower in men than women [10, 14]. Men who take erythromycin therefore have further reduced levels of CYP3A4 activity and ability to clear xenobiotics typically cleared by CYP3A4. Because erythromycin is not believed to be directly carcinogenic [15], our results suggest that the presence of CYP3A4-metabolized substances may potentially have a role in MM etiology. Moreover, Burns and colleagues report recently [16] an acquired loss of CYP2C19 activity among MM patients following diagnosis, and the effect exhibits a similar sex difference in their cohort (44% of males and 0% of females, p=0.027). These data support the need for further research of enzymes in the CYP family in understanding their role in MM etiology and progression.

Of note, prednisolone, the active metabolite of the steroid hormone prednisone, is another CYP3A4-metabolized substance. Prednisone use was associated with an over fourfold increased MM risk in a Connecticut case-control study of women [4]. We hypothesize that an association between prednisone use and MM risk would have been observed among men. Unfortunately, prednisone use was not queried separately from use of other steroids in the LAMMCC questionnaire and we could not evaluate this association.

Based on case reports [17–19], phenytoin use has historically been linked with MM risk, but multiple case-control studies conducted since then have not corroborated this association [7, 20]. While we note based on the low prevalence of phenytoin use in the LAMMCC an

elevated but not statistically significant link between phenytoin use and MM risk, we encourage further evaluation of this question in future prospective studies.

Finally, we note the observed association between sulfonamide use and MM risk among blacks. Although based on small numbers, this association may provide indirect clues regarding higher MM risk among blacks. Specifically, sulfonamide use intensifies the destruction of red blood cells, particularly in individuals with glucose-6-phosphate dehydrogenase deficiency, a condition more common among blacks than whites [21]. Further investigation into the role of sulfonamide use in MM etiology may thus also be warranted.

Our study has several limitations. Data in the LAMMCC for medication use are based on self-report and were not validated via examination of medical records. Moreover, because the period of time in which erythromycin was used was not assessed in the LAMMCC, we could not exclude recent usage with respect to date of MM diagnosis. However, the LAMMCC did have dates of recent infections for which antibiotics such as erythromycin would have been considered (e.g., with respiratory infections, strep throat, bladder infection, pneumonia). While we note that the LAMMCC questionnaire did not include all infections for which erythromycin may have been indicated, even with the available exclusions up to five years, our association between erythromycin and MM risk remained consistent. This is especially important as monoclonal gammopathy of undetermined significance (MGUS) regularly precedes MM diagnosis [22] and is itself accompanied with increased risk of various infections and conditions [23]. Landgren and colleagues recently report a statistically significant association (OR=1.7) between history of pneumonia (restricted to five years before MM diagnosis) and MM in a large Danish case-control study [24], and so medication use in the LAMMCC could be a proxy for this association. However, by accounting for infections prior to MM diagnosis in sensitivity analysis, we reduced the potential for protopathic bias that has been previously described [25].

In summary, we report a nearly twofold risk for MM with erythromycin use in a population of Los Angeles County residents, which rises with increasing numbers of treatment courses and is more pronounced in men. These data add to the sparse literature on MM risk factors and suggest a potential role for the CYP-family genes and metabolized substances in MM risk. The increased MM risk observed with sulfonamide use among blacks further suggests that drug metabolism may be a fruitful area of pursuit for illuminating potential mechanisms in MM etiology. We encourage future large-scale consortial efforts, especially in prospective studies less susceptible to protopathic or recall bias, to evaluate the role of CYP3A4-metabolized drugs and other mechanisms of drug metabolism in risk of MM and its precursor, MGUS.

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 County Multiple Myeloma Case-Control (LAMMCC) Study, 1985–1992.

	Men		Women	
	Cases (*n*=152) *n* (%)	**Controls (*n*=152) *n* (%)**	**Cases (*n*=126) *n* (%)**	**Controls (*n*=126) *n* (%)**
Race				
White	112 (73.7)	114 (75.0)	75 (59.5)	75 (59.5)
Black	21 (13.8)	21 (13.8)	39 (31.0)	39 (31.0)
Hispanic	17 (11.2)	16 (10.5)	11 (8.7)	11 (8.7)
Other	2 (1.3)	1 (0.7)	1 (0.8)	1 (0.8)
Age at interview (years)				
Under 45	8 (5.3)	8 (5.3)	5 (3.9)	3 (2.4)
45–54	21 (13.8)	14 (9.2)	17 (13.5)	15 (11.9)
55–64	51 (33.5)	50 (32.9)	36 (28.6)	36 (28.6)
65–74	65 (42.8)	65 (42.8)	62 (49.2)	60 (47.6)
75+	7 (4.6)	15 (9.8)	6 (4.8)	12 (9.5)
Age at diagnosis (years)				
Under 45	10 (6.6)		6 (4.8)	
45–54	22 (14.5)		22 (17.5)	
55–64	58 (38.1)		40 (31.7)	
65–74	60 (39.5)		58 (46.0)	
75+	2 (1.3)		0 (0.0)	
Education				
Some high school or less	26 (17.1)	26 (17.1)	26 (20.6)	34 (27.0)
High school graduate	28 (18.4)	32 (21.1)	47 (37.3)	37 (29.3)
Some college or more	97 (63.8)	94 (61.8)	52 (41.3)	55 (43.7)
Unknown	1 (0.7)	0 (0.0)	1 (0.8)	0 (0.0)

Table 2

Past medication use and risk of MM in the Los Angeles County Multiple Myeloma Case-Control (LAMMCC) Study, 1985–1992, among all participants.

		Cases (*n*=278)^ *n* (%)	Controls (*n*=278)^ *n* (%)	OR (95 % CI)
Amphetamines	no	256 (93.8)	250 (91.6)	1.00 (ref)
	yes	17 (6.2)	23 (8.4)	0.72 (0.38–1.38)
Antibiotics				
Erythromycin	no	214 (81.4)	234 (89.0)	1.00 (ref)
	any	49 (18.6)	29 (11.0)	**1.85 (1.13–3.03)**
	1 course	14 (5.3)	15 (5.7)	1.02 (0.48–2.16)
	2+ courses	35 (13.3)	14 (5.3)	**2.73 (1.43–5.22)**
				p-trend = 0.003
Penicillin or ampicillin	no	111 (42.0)	102 (38.6)	1.00 (ref)
	yes	153 (58.0)	162 (61.4)	0.87 (0.61–1.23)
Tetracycline	no	174 (68.5)	182 (71.7)	1.00 (ref)
	yes	80 (31.5)	72 (29.3)	1.16 (0.79–1.70)
Non-insulin antidiabetics	no	261 (94.2)	259 (93.5)	1.00 (ref)
	yes	16 (5.8)	18 (6.5)	0.88 (0.44–1.77)
Benzodiazepines	no	206 (74.6)	198 (71.7)	1.00 (ref)
	yes	70 (25.4)	78 (28.3)	0.86 (0.59–1.26)
Gout medication	no	258 (93.1)	263 (94.9)	1.00 (ref)
	yes	19 (6.9)	14 (5.1)	1.38 (0.68–2.82)
NSAIDs*				
Indometacin	no	256 (93.4)	254 (92.7)	1.00 (ref)
	yes	18 (6.6)	20 (7.3)	0.89 (0.46–1.73)
All other NSAIDs	no	219 (80.0)	213 (77.7)	1.00 (ref)
	yes	55 (20.0)	61 (22.3)	0.87 (0.58–1.32)
Phenytoin	no	264 (97.1)	269 (98.9)	1.00 (ref)
	yes	8 (2.9)	3 (1.1)	2.71 (0.71–10.34)
Steroids‡	no	193 (71.2)	191 (70.5)	1.00 (ref)
	yes	78 (28.8)	80 (29.5)	0.97 (0.67–1.40)
Sulfonamides	no	215 (81.4)	232 (87.9)	1.00 (ref)
	yes	49 (18.6)	32 (12.1)	**1.65 (1.02–2.68)**

^ Numbers may not add up due to unknown usage;

* Non-steroidal anti-inflammatory drugs;

‡ Cortisone, prednisone, celestone, or betamethasone