

A Case-Control Study of Multiple Myeloma in Whites: Chronic Antigenic Stimulation, Occupation, and Drug Use¹

Martha S. Linet,² Siobán D. Harlow, and Joseph K. McLaughlin

Department of Epidemiology, Johns Hopkins School of Hygiene and Public Health, Baltimore, Maryland 21205 [M. S. L., S. D. H.]; and Biostatistics Branch, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland 20892 [J. K. M.]

ABSTRACT

A hospital-based case-control study of multiple myeloma in whites (100 cases and 100 controls from seven Baltimore hospitals) was conducted to examine a number of postulated risk factors. Cases and controls were matched on age, sex, hospital, and year of diagnosis. Distributions by marital status and religious affiliation were found to be similar. Educational levels of cases were similar to controls except for postcollege schooling, where there was a slight excess of cases (6%) compared to controls (3%). No statistically significant associations were found between multiple myeloma and prior history of medical conditions believed to cause prolonged stimulation of the immune system including chronic bacterial infections [odds ratio (OR) = 0.8], autoimmune disorders (OR = 1.0), allergy-related disorders (OR = 1.0), or lymphoid tissue surgery (OR = 1.2). Statistically significant positive associations were found for occupational exposure to petroleum products (OR = 3.7; 1.3-10.3) and asbestos (OR = 3.5; 1.0-12.0). No increased risk was found for cigarette smoking or alcohol consumption or for employment in a variety of industries and occupations implicated in earlier studies. A significantly elevated risk was found for prior use of laxatives (OR = 3.5; 1.1-11.1), and elevated (OR \geq 1.8) but nonsignificant risks were found for use of other medications including diphenylhydantoin, phenobarbital, diazepam, propranolol, ibuprofen, and diet drugs and stimulants. These findings require clarification in larger, population-based studies.

INTRODUCTION

Although multiple myeloma accounts for only 1.1% of all malignancies in whites and 2.1% in blacks in the United States (1), this lymphopoeitic malignancy is of great epidemiological interest because of the apparent striking increase in incidence and mortality over the past three decades (2-5). This may be due to improvements in diagnosis or increased access to medical care, or may represent a true rise in incidence. Because of the general demographic trend of aging occurring in the United States and many other western nations, this malignancy, whose incidence is highest in the oldest age groups, is expected to become an increasingly important cause of cancer deaths. A number of risk factors have been associated with multiple myeloma including chronic antigenic stimulation, solvents used in the petrochemical and synthetic rubber industries, ionizing radiation, employment in farming, cosmetology, a number of other manufacturing industries, and familial and genetic factors (3). Most of these postulated risk factors have been suggested from case reports. The few analytical investigations of putative environmental risk factors for multiple myeloma (6-9) have resulted in somewhat contradictory findings; thus, we initiated a hospital-based case-control study to evaluate a number of the hypothesized associations.

Received 7/17/86; revised 1/13/87; accepted 3/3/87.

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¹ This investigation was supported by Biomedical Research Support Grant 2-SO7-RR05445-22 and in part by U. S. Public Health Service Grant RO1-CA33822 from the Division of Extramural Activities, National Cancer Institute.

² To whom requests for reprints should be addressed, at Department of Epidemiology, School of Hygiene and Public Health, The Johns Hopkins University, 615 North Wolfe Street, Baltimore, MD 21205.

PATIENTS AND METHODS

Cases of multiple myeloma (International Classification of Diseases, Eighth Revision Code 203 and Ninth Revision Code 203) were ascertained from seven Baltimore area hospitals for the period January 1, 1975, to December 31, 1982. Cases were restricted to whites who were residents of the area at the time of diagnosis. The seven hospitals were selected to include both community and university hospitals.

All cases were reviewed by a physician-epidemiologist (M. S. L.) using the case definition for multiple myeloma proposed by the Chronic Leukemia-Myeloma Task Force of the National Cancer Institute (10). Diagnostic criteria included: a malignant proliferation of plasma cells and presence of a serum or urinary myeloma paraprotein. In the absence of a serum or urinary myeloma protein, a potential myeloma case was considered to meet the study criteria if there was radiological evidence of osteolytic lesions or palpable tumors, plus one or more of the following: marrow plasmacytosis of more than 20% in aspirate or biopsy specimens from two sites (excluding reactive plasmacytosis) and/or tissue biopsy specimens demonstrating replacement and distortion of normal tissue by plasma cells.

Controls were individually matched to cases on hospital, age (± 5 years), sex, and year of diagnosis. For each interviewed case one of 11 hospital discharge diagnosis categories of diseases was randomly chosen, and, using a random starting point within the disease category listing, the first individual who met the matching criteria was selected. The following diagnoses were excluded from eligibility: all cancers, diseases of blood-forming organs, mental disorders, obstetrical conditions, and congenital anomalies. If a matched control could not be found within a given category, another diagnostic category was randomly chosen. Fifteen % of the controls had circulatory diseases, 13% digestive diseases, 13% nervous system and sense organ diseases, 13% accidents/violence/poisonings, 12% genitourinary diseases, 9% respiratory diseases, 5% musculoskeletal diseases, 5% skin and s.c. system diseases, 5% endocrine diseases, 4% infectious and parasitic diseases, and 6% others.

A standardized questionnaire was administered by telephone to the study subject, or, if that individual had died or was otherwise not able to be interviewed, information was sought from the closest possible next of kin. Areas assessed in the interview were: sociodemographic characteristics; prior history of chronic bacterial infectious diseases, connective tissue and autoimmune conditions, allergic disorders, surgical excision of lymphoid tissue, and other medical history; history of medications used; occupations, occupational and environmental exposures; and tobacco and alcohol habits.

A matched-pairs analysis was used with the relative risk of multiple myeloma estimated by the odds ratios (11). Exact confidence limits were computed whenever the total number of discordant pairs was less than 20 (11), and approximate confidence intervals, based on the normal approximation, were calculated whenever the discordant pairs were greater than or equal to 20 (12).

Analysis of prior medical conditions was restricted to those occurring at least 5 years prior to diagnosis. Due to insufficient data about specific dates of occupational exposure and medication use, occupational exposures and drug use occurring prior to diagnosis were analyzed.

Risk factors were separately evaluated for males and females, but virtually no major differences by sex were found, thus results are presented for both sexes combined. There were no major differences observed for matched pairs identified at university hospitals compared with those diagnosed at community hospitals. Because of the differences in proportions of directly interviewed cases and controls, source of data (subject respondent *versus* next of kin) was adjusted for in a matched

Table 1 Acquired immune-related disorders and multiple myeloma

Acquired immune-related disorders ^b	b/c ^c	Crude		Adjusted ^d		N ^d
		Matched OR	95% CI	Matched OR	95% CI	
Chronic bacterial infections ^e	11/16	0.7	(0.3-1.5)	0.8	(0.3-1.8)	93
Autoimmune disorders ^f	8/5	1.6	(0.5-6.2)	1.0	(0.3-3.6)	93
Allergy-related disorders ^g	17/21	0.8	(0.4-1.5)	1.0	(0.5-2.3)	77
Lymphoid tissue surgery ^h	19/25	0.8	(0.4-1.4)	1.2	(0.6-2.6)	93

^a Adjusted for respondent status.
^b Conditions occurring at least 5 years prior to diagnosis.
^c Consists of matched pairs in which a subject had a prior history of at least one condition in each group of acquired immune related disorders. b/c, discordant pairs ratio.
^d Total number of pairs for which data was available for both members of pair.
^e Includes tuberculosis, osteomyelitis, pyelonephritis, chronic bronchitis, chronic sinusitis, and syphilis.
^f Includes rheumatoid arthritis, psoriasis, systemic lupus erythematosus, Reiter's syndrome, ankylosing spondylitis, Sjogren's disease, dermatomyositis, scleroderma, autoimmune hemolytic anemia, thrombocytopenic purpura, Hashimoto's disease, Grave's disease, pernicious anemia, and rheumatic fever.
^g Includes hay fever, asthma, eczema, recurrent hives, insect sting allergy, and treatment with desensitization injections.
^h Includes tonsillectomy, adenoidectomy, appendectomy, splenectomy, and thymectomy.

conditional logistic regression analysis (11). As a result of small numbers comprising some of the discordant pair ratios, adjustment for respondent status was not possible for a number of occupational exposures and medications. Thus, results are presented both adjusted and unadjusted.

RESULTS

We identified 121 subjects who met the case definition criteria. Interviews were obtained for 100 (83%) of these cases; of the nonparticipants, 15 refused, four could not be traced, and two were due to physician refusals. For each of the interviewed cases an age-, sex-, hospital-, and year-of-diagnosis-matched control was selected. A total of 146 eligible controls were approached in order to achieve 100 matched pairs. Among the 46 nonparticipating controls, 34 refused, six could not be traced, and six were due to physician refusal. There were no statistically significant differences between participating and nonparticipating cases or controls for age, sex, or type of hospital (or in discharge diagnoses for participating and nonparticipating controls).

Nineteen of the 22 living cases were directly interviewed; for three too ill to be interviewed and 78 who had died, next of kin were interviewed of whom 40% were spouses, 37% children, and 23% sibs and other relatives. Of the 100 controls, 53 were directly interviewed, and next-of-kin interviews were obtained for 47 (consisting of 25% spouses, 47% children, and 28% sibs and other relatives).

Twenty-two % of the cases were less than 60 years of age, 50% were 60-75, and 28% older than 75; 45% of cases and controls were males. There were no appreciable differences between cases and controls for marital status or religious affiliation. In general there was little difference for educational attainment between cases and controls, except at the highest educational levels where 6% of cases and 3% of controls had received postcollege schooling. No association was found for ever having smoked cigarettes (OR³ = 0.8; 95% CI = 0.4-1.6), consumed beer (OR = 0.8; 0.4-1.6), or consumed hard liquor (OR = 1.7; 0.9-3.3).

The relationship between multiple myeloma and prior history of acquired immune-related disorders is shown in Table 1. The odds ratios were not significantly different than 1.0 for chronic or subacute bacterial infections, autoimmune disorders, allergy-

related disorders, and surgical excision of lymphoid tissue.

Employment in several industries and occupations was evaluated as a result of positive associations reported in earlier studies. No significantly elevated risk was observed for ever being employed in any of the following industries: agriculture, chemical, textile, lumber and wood, furniture, paper, printing, rubber, construction, manufacturing, mining, personal services, professional and related services, and public administration. The following occupations also did not show a significantly increased risk of multiple myeloma: farmers and farm managers, farm laborers, foresters and conservation workers, carpenters, painters, printers, professional and technical workers, and craftsmen and kindred workers. The numbers of cases and controls, however, in several of the industrial and occupational categories were quite small.

In addition, a number of occupational exposures suspected of being associated with increased risk of multiple myeloma were directly enquired about in the questionnaire (Table 2). Statistically significant odds ratios were found for exposure to petroleum and to asbestos. Due to small numbers and incomplete data, the effect of duration of exposure on the risk of multiple myeloma could not be evaluated.

Table 3 shows associations between prior use of medications and multiple myeloma. A significantly elevated risk was found for use of laxatives and nonsignificantly elevated risks (OR ≥ 1.8) were found for prior use of diphenylhydantoin, phenobar-

Table 2 Occupational exposures and multiple myeloma

Exposure ^b	b/c ^c	Crude		Adjusted ^d		N ^d
		Matched OR	95% CI	Matched OR	95% CI	
Benzene	8/7	1.1	(0.4-3.7)	1.2	(0.4-3.6)	65
Cutting oil	11/5	2.2	(0.7-8.1)	2.7	(0.8-9.3)	71
Petroleum	20/6	3.3	(1.3-8.3)	3.7	(1.3-10.3)	90
Arsenic	4/3	1.3	(0.2-9.1)	— ^e	—	78
Lead	10/9	1.1	(0.4-3.1)	1.1	(0.4-3.0)	64
Chromate	3/1	3.0	(0.2-157.5)	—	—	88
Mercury	1/3	0.3	(0.0-4.2)	—	—	83
Asbestos	13/4	3.3	(1.0-13.7)	3.5	(1.0-12.0)	70

^a Adjusted for respondent status.
^b Occupational exposure prior to diagnosis.
^c b/c, discordant pairs ratio.
^d Total number of pairs for which data was available for both members of pair.
^e Adjustment not possible due to small numbers.

Table 3 Use of selected medications and multiple myeloma

Type of medication ^b	b/c ^c	Crude		Adjusted ^d	
		Matched OR	95% CI	Matched OR	95% CI
Diphenylhydantoin	3/0	∞	(0.6-∞)	— ^d	—
Phenobarbital	2/0	∞	(0.3-∞)	—	—
Diazepam	6/3	2.0	(0.4-12.4)	—	—
Chlordiazepoxide	2/2	1.0	(0.1-13.8)	—	—
Propranolol	9/5	1.8	(0.5-6.8)	0.9	(0.3-3.1)
Hydrochlorothiazide	4/4	1.0	(0.2-5.4)	—	—
Furosemide	2/5	0.4	(0.0-2.4)	—	—
Methyldopa	3/5	0.6	(0.1-3.1)	—	—
Digoxin	3/5	0.6	(0.1-3.1)	—	—
Nitroglycerin	4/3	1.3	(0.2-9.1)	—	—
Ibuprofen	6/3	2.0	(0.4-12.4)	—	—
Phenylbutazone	0/1	0	(0.0-19.0)	—	—
Indomethacin	1/2	0.5	(0.0-9.6)	—	—
Diet pills and stimulants (not further specified)	4/1	4.0	(0.4-197.0)	—	—
Maalox	8/5	1.6	(0.5-6.2)	1.3	(0.4-4.5)
Vitamin C	10/7	1.4	(0.5-4.4)	1.1	(0.4-3.6)
Multivitamins	16/12	1.3	(0.6-2.8)	1.2	(0.5-2.8)
All laxatives	17/4	4.3	(1.4-12.6)	3.5	(1.1-11.1)

^a Adjusted for respondent status.
^b Medications used prior to diagnosis.
^c b/c, discordant pairs ratio.
^d Adjustment not possible due to small numbers.

³ The abbreviations used are: OR, odds ratio; CI, confidence interval.

bital, diazepam, propranolol, nitroglycerin, ibuprofen, and diet drugs and stimulants (not further specified).

DISCUSSION

A number of earlier clinical reports suggested that there was an increased risk of multiple myeloma occurring in persons with a variety of prior chronic bacterial infectious diseases (13–16), autoimmune disorders (15–18), and allergic conditions and allergic hyposensitization therapy (13, 14, 19, 20). A recent case-control study by Gallagher *et al.* (6) reported a statistically significant positive association for prior history of allergies, allergy treatments, and myxedema; they found no association for other chronic bacterial diseases, autoimmune disorders, or tonsillectomy. We found no association between multiple myeloma and prior history of chronic bacterial infectious disorders, allergy-related disorders, and surgical excision of several types of lymphoid tissue. Results of other recent case-control studies of multiple myeloma⁴ and of related lymphoproliferative diseases [non-Hodgkin's lymphoma (21) and chronic lymphocytic leukemia (22)], also have not supported the hypothesis that prolonged stimulation of the immune system is causally related to an increased risk of lymphoproliferative malignancies.

Excess risks of multiple myeloma have previously been reported for employment in farming and agriculture (6, 9, 23–28), chemical manufacturing plants (29, 30), the painting industry (8), lumber, wood furniture, and paper industries (8, 28–31), textile plants (29), the rubber industry (32, 33), cosmetology (34, 35), printing plants (36), mining (29), and a number of other industries (37). Comparison of employment histories of cases and controls in our study did not confirm these reports. However, the absence of significant findings may reflect the lack of sufficient statistical power to detect differences due to our small sample size and the absence of some of these industries in the Baltimore area. Relationships with several chemical, metal, fiber and dust materials (7, 28–43) were explored through questions about occupational exposures. The significantly elevated risk found for exposure to petroleum products confirms earlier reports of a multiple myeloma excess among petroleum-exposed workers (40, 41). The finding for exposure to asbestos may be noteworthy, since it is consistent with earlier clinical reports suggesting that asbestos-related immunologic abnormalities (defective cell-mediated immunity and hyperactivity of B cell function) are causally related to an increased risk of lymphoproliferative neoplasms (38, 39). We did not find associations with exposure to pesticides, paints, paint-related products, plastics, elastomers, carbon monoxide, or a variety of metals, as recently reported by Morris *et al.* (7).

The elevated risk for prior use of diphenylhydantoin confirms earlier case reports (44, 45). In reviewing reports of diphenylhydantoin and lymphoproliferative malignancies, Matzner and Polliack note that this anticonvulsant may suppress cellular and humoral immune responses (44). Friedman (8), however, found no association with diphenylhydantoin in a recently conducted case-control study of myeloma. The statistically significant association we found for laxative use is intriguing, although it may suggest an underlying poor bowel motility due to early neoplastic or amyloid infiltration, or some other disease-related effect. Also of interest is the excess noted for prior use of diet pills and stimulants. A strong association between amphetamine use and Hodgkin's disease has been reported in two case-control investigations (46, 47), although we are una-

ware of any reports specifically linking amphetamine use with multiple myeloma. The excess risks found for several types of medications in our study may not be directly associated with the drugs themselves, but with underlying conditions for which the drugs were prescribed. However, we did not have sufficient information to explore this hypothesis.

We found no significant differences between cases and controls for marital status, religious affiliation, cigarette use, or alcohol consumption. Our finding of an excess of cases with postcollege education compared with controls is consistent with earlier investigations reporting a higher level of education among the cases (48, 49). These results contrast with a report by Johnston *et al.* (50) showing no association with education or other indicators of socioeconomic status.

This hospital-based investigation of multiple myeloma in whites has identified a number of intriguing clues which require further clarification in larger, population-based studies.

ACKNOWLEDGMENTS

We are grateful to Florence Kramer for interviewing the study subjects and Thelia Barnes for help in the preparation of this manuscript.

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⁴ S. Grufferman, personal communication.

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