

Antigenic Stimulation and Multiple Myeloma

A Prospective Study

Claire C. Bourguet, Ph.D., and Everett E. Logue, Ph.D.

Background. A causal relationship between antigenic conditions and multiple myeloma was suggested by case reports. Although controlled studies identified associations with individual conditions, they failed to give overall support to the hypothesis. Using a prospective cohort representative of the U.S. population, the authors hypothesized that immune-stimulating conditions are a risk factor for multiple myeloma.

Methods. The First National Health and Nutrition Examination Survey cohort of 14,407 persons were interviewed from 1971 to 1975 by the National Center for Health Statistics. Vital status with cause of death and hospitalizations were ascertained from 1982 to 1985 and in 1986. From the initial questionnaire, four risk factors were constructed: allergies (asthma, hives, hay fever, food allergies, and other allergies); autoimmune conditions (arthritis, thyroid disease and/or medication, rheumatic fever, diabetes, pernicious anemia); chronic bacterial conditions (chronic bronchitis or emphysema, chronic cough, tuberculosis, ulcers); and inflammatory conditions (gout, gallstones, recurrent or chronic enteritis, pleurisy).

Results. Eighteen multiple myeloma (MM) cases were documented. The rate ratio (RR) of MM increased as the number of reported inflammatory conditions increased (one condition, RR = 2.0, 95% confidence interval [CI] = 1.2–3.3; 2 or more conditions, RR = 4.3, 95% CI = 1.5–12.4). The RR of myeloma also increased ($P = 0.0002$) with time since start of inflammatory conditions (RR = 1.6 for every 10 years of exposure). When cases were restricted to those with more than five years of follow-up, myeloma risk increased with the number of inflammatory conditions (two conditions, RR = 4.6, 95% CI = 1.5–13.8).

Conclusions. Although the number of cases is small and exposure may be misclassified, the prospective nature of the study design strengthens the results of the study. *Cancer* 1993;72:2148–54.

Key words: multiple myeloma (etiology), antigens, allergens, bacterial infections, inflammation, autoimmune diseases, prospective studies.

Multiple myeloma is a malignant neoplasm of plasma cells. The monoclonal origin of malignant plasma cells is accepted on the basis of the homogeneity of the secreted immunoglobulin.^{1,2} There is increasing evidence that the initial malignant transformation occurs in a cell that is a precursor to both B-lymphocytes and T-lymphocytes. Multiple myeloma develops in a multistep process starting with a monoclonal gammopathy of undetermined significance, a benign proliferation of monoclonal cells. In some patients, monoclonal gammopathy of undetermined significance progresses to symptomatic multiple myeloma.² Etiologic factors governing the initiation and subsequent progression to clinically apparent myeloma remain unknown.

A causal relationship between antigenic conditions and multiple myeloma was originally suggested on the basis of case reports that identified concurrent disease in myeloma cases.^{3–5} Although controlled studies have identified associations with individual conditions that cause chronic or recurrent stimulation of the immune system, they have failed to support a unified mechanism.

Several case-control studies of the antigenic stimulation hypothesis of multiple myeloma have relied on hospital-based control groups. These control groups are susceptible to selection factors that may mask a true association of myeloma with other medical conditions. In the current study, we used the First National Health and Nutrition Examination Survey (NHANES I) cohort to examine prospectively the hypothesis that chronic or

Presented in part at the Society for Epidemiologic Research, Buffalo, New York, June 1991.

From the Division of Community Health Sciences, Northeastern Ohio Universities College of Medicine, Rootstown, Ohio.

The authors thank Richean Kuzior for preparing multiple drafts of the manuscript.

Address for reprints: Claire C. Bourguet, Ph.D., Northeastern Ohio Universities College of Medicine, P.O. Box 95, Rootstown, OH, 44272.

Accepted for publication May 10, 1993.

recurrent conditions that stimulate the immune system are risk factors for multiple myeloma.⁶

Methods

The data for the study come from the NHANES I Epidemiologic Follow-up Study, which was conducted by the National Center for Health Statistics. The NHANES I cohort consists of a probability sample of the civilian noninstitutionalized U.S. population.^{6,7}

The NHANES I baseline questionnaire was completed from 1971 to 1975 during face-to-face interviews with each study member. Two waves of follow-up data were subsequently collected, the first from 1982 to 1984 and the second in 1986. At both follow-up waves, vital status was determined and death certificates were obtained for deceased cohort members. Living cohort members or proxies were reinterviewed.

In the 1982–84 follow-up, 14,407 participants, age 25 to 74 years at the time of the NHANES I, were contacted. Cohort members or a proxies responded to a 2-hour personal interview.⁸ In 1986, 3,980 cohort members age 55 years or older at the initial interview and who were still alive at the 1982–84 follow-up were contacted. A half-hour telephone interview was conducted with each member.⁹

At the time of the follow-up interview, each cohort member or proxy was asked to list all episodes of hospitalization. Respondents authorized release of medical records to the National Center for Health Statistics for the purposes of the study.^{8,9} Details of the hospitalization, including the discharge summary, were requested from each hospital.

For the current study, the hospitalization data and the death certificate data were used to identify the members with multiple myeloma. All diagnoses listed for each hospitalization and all cause-of-death codes were searched for International Classification of Diseases code 203 (MM). Date of hospitalization for multiple myeloma was used as the best available surrogate for date of diagnosis. If date of hospitalization was not available, date of death was used.

The NHANES I (1971–75) questionnaire included a standardized medical history covering various topics. The health-condition list was used to construct four a priori categories of conditions that result in chronic or recurrent stimulation of the immune system: (1) allergic conditions—asthma, hives, hay fever, food allergies, and other allergies; (2) autoimmune conditions—arthritis, rheumatic fever, diabetes, thyroid disease and/or medication, and pernicious anemia; (3) chronic bacterial conditions—tuberculosis, chronic bronchitis or emphysema, chronic cough, and ulcers; and (4) inflamma-

tory conditions—gout, gallstones, pleurisy, and recurrent or chronic enteritis. The interview ascertained the presence of each disease condition at time of interview, a history of a condition no longer present, and the time since the person first had the condition. The Appendix shows the questionnaire items that were used to construct each category.

To control for confounding factors by age and year of birth and to reduce computer processing time, we restricted the data analyses to cohort members who were born in the same study years as the persons with multiple myeloma. Crude incidence rate ratios (RR) associated with a history of allergic, autoimmune, chronic bacterial, or inflammatory conditions were calculated. Incidence RR and 95% confidence intervals adjusted for potential confounders were estimated using a proportional hazards model by means of the PHGLM procedure in the SAS (Cary, NC) statistical software.^{10,11}

For the data analysis, the risk factors were structured to indicate a disease category present at any time before or at the time of interview, present at the time of the interview, and total time since initiation of the medical conditions in the category. Although all persons with myeloma had denied any malignant tumor at the baseline interview, the possibility of prevalent myeloma at the time of interview exists. Consequently, the data were reanalyzed after restricting the cases to those persons who had 5 or more years of follow-up after the baseline interview.

After two waves of follow-up, 94% of the cohort had been traced and their vital status was known. Ninety-seven percent of the death certificates were obtained for the 2,657 cohort members who had died. From 1982 to 1984, 93% of the surviving respondents were interviewed, and in 1986, 97% of the survivors were reinterviewed.⁹

The completeness of the hospitalization data can only be estimated, because cohort members may have reported hospitalizations that did not fall within the eligible follow-up period. However, from 1982 to 1984, no hospital record was obtained for 22% of persons who reported at least one hospitalization.^{8,12} In 1986, the hospital records could not be obtained for 28% of the reported hospitalization episodes.⁹

Results

Eighteen cases of multiple myeloma were found in the NHANES I cohort. Nine cases were identified by both hospital and death records, eight cases by hospital records only, and one case by death certificate only.

Table 1. Descriptive Characteristics of Multiple Myeloma Cases and Selected NHANES I Cohort Members

	MM Cases (N = 18)		Cohort (N = 2823)	
	n	%	n	%
Sex				
Male	6	33	1273	45
Female	12	67	1550	55
Race				
White	15	83	2392	85
Nonwhite	3	17	431	15
Education				
Grammar school	15	83	1258	45
High school	3	17	1099	39
Any college	0	0	466	17
Age at interview (yr)				
Mean	64.8		63.2	
Range	41.3-74.6		37.5-75.2	
Yr of follow-up				
Mean	6.8		10.1	
Range	0.7-13.5		0.02-15.2	

NHANES I: First National Health and Nutrition Examination Survey; MM: multiple myeloma.

After adjusting for the year-of-birth restriction, the cohort included 2,823 persons who did not develop myeloma. Table 1 shows the descriptive characteristics of the 18 multiple myeloma cases in contrast to the remainder of the cohort. The MM cases were more likely to be women, less educated, and had a shorter mean length of follow-up than the cohort. The racial distribution of the cases was similar to the cohort.

Table 2 shows the multiple myeloma rate per 10,000 person-years of follow-up and the RR associated with sex, race, and education. The confidence

Table 2. Multiple Myeloma Rates and Crude Rate Ratios According to Demographic Characteristics

	n	Rate/10,000 person-yr	Rate ratio	95% CI
Sex				
Female	1562	7.23	1.5	0.6-3.7
Male	1279	4.95	1.0	
Race				
Nonwhite	434	6.94	1.1	0.3-4.1
White	2407	6.15	1.0	
Education				
Grammar school	1273	12.08	6.6	2.6-16.7
High school	1102	2.64	1.0	
Any college	466	0.00	—	

CI: confidence interval.

Table 3. Incidence Rate Ratios for Multiple Myeloma According to Antigenic Condition Reported at Baseline Interview

	Cases/person-yr of follow-up	Rate ratio*	95% CI
Allergies			
≥ 2 (mean = 2.4)	2/2646	3.4	0.04-285.77
1	5/5406	1.7	0.26-10.55
0	11/20667	1.0	
Autoimmune conditions			
≥ 2 (mean = 2.7)	4/3717	2.5	0.94-6.64
1	7/10,464	1.4	0.98-2.02
0	7/14,538	1.0	
Chronic bacterial infection			
≥ 2 (mean = 2.2)	0/2152	0.1	0.01-2.33
1	2/4734	0.4	0.11-1.47
0	16/21,833	1.0	
Inflammatory conditions			
≥ 2 (mean = 2.1)	7/2823	4.3	1.52-12.41
1	1/3984	2.0	1.22-3.32
0	10/21,912	1.0	

CI: confidence interval.

* Adjusted for education using a proportional hazards model. The rate ratio was calculated for the mean exposure in the exposure level.

intervals indicated that the higher myeloma rates among women and nonwhites may have been produced by random variation. A grammar school education was associated with an elevated RR (RR = 6.6, $P < 0.01$). Education was included in subsequent mathematical models as a potential confounder. Because of the year-of-birth restriction in the study design, age was not a predictor of myeloma risk in these data.

Table 3 shows the incidence RR for multiple myeloma associated with a cohort member's report that he or she had ever had one or more of the grouped antigenic conditions. Inflammatory conditions showed a statistically significant association ($P < 0.01$) of increasing RR with increasing number of conditions. Allergies and autoimmune conditions showed a dose-response relationship. These associations, however, were not statistically significant. Chronic bacterial conditions were inversely associated with multiple myeloma risk, although the association was compatible with random variation ($P = 0.17$).

Parallel data analyses were conducted using, as the indicator of exposure, the cohort member's response that he or she had the condition at the time of the NHANES I interview. The pattern of association was similar to that shown in Table 3, although the strength of the associations was reduced due to the smaller number of persons reporting current disease. The incidence RR associated with autoimmune conditions present

Table 4. Rate Ratios for Multiple Myeloma in Relationship to Increasing Time Since Start of Antigenic Condition

	Years since start		Rate ratio*		P value†
	Mean	SD	5 yr	10 yr	
Allergies					
Myeloma cases	9.6	15.5			
Cohort	8.0	20.0	1.0	1.1	0.62
Autoimmune conditions					
Myeloma cases	12.0	19.7			
Cohort	7.7	14.6	1.1	1.2	0.18
Chronic bacterial infection					
Myeloma cases	0.9	2.8			
Cohort	5.1	14.9	0.7	0.5	0.28
Inflammatory conditions					
Myeloma cases	13.9	23.8			
Cohort	4.3	10.7	1.3	1.6	0.0002

SD: standard deviation.

*Rate ratio for 5 and 10 years of exposure compared with no exposure from proportional hazards model.

†From test of statistical hypothesis (H_0): $H_0: \beta = 0$ where β is the coefficient for a single year of additional exposure.

at the time of interview was significantly elevated (one condition, RR = 1.6; two conditions, RR = 2.7; $P = 0.04$).

Table 4 shows the reported length of time since the cohort member initially suffered from the condition. This exposure variable only approximates duration of exposure, because there is no information that a condition was present continuously after initiation. Compared with other cohort members, the mean times since initial exposure reported by persons with myeloma were longer for allergic, autoimmune, and inflammatory conditions. For inflammatory conditions, there was a statistically significant increase ($P = 0.0002$) in risk with increasing time since first exposure (RR = 1.6 for each additional 10 years since the start of the inflammatory condition).

Four persons with myeloma had been first hospitalized for multiple myeloma within 5 years of the interview. One person was diagnosed with myeloma within 1 year of the interview. Because undiagnosed disease may have been present at the interview, these four cases were excluded and the analyses were repeated. The association of inflammatory conditions with multiple myeloma risk was strengthened (one condition, RR = 2.1, 95% confidence interval = 1.2–3.7; two conditions, RR = 4.6, 95% confidence interval = 1.5–13.8). In this analysis, an RR of 1.9 ($P = 0.001$) was associated with an inflammatory condition initiated 10 or more years before the interview. The association with allergic conditions was also strengthened, although it was not statistically significant (one condition, RR = 2.2; two conditions, RR = 4.9; $P = 0.39$). In this analysis, neither

bacterial nor autoimmune conditions showed an association with myeloma.

Discussion

Previous studies of the antigenic stimulation hypothesis for the etiology of multiple myeloma are difficult to interpret. Prospective data have been reported from the rheumatoid arthritis cohort of Isomaki et al.¹³ and from the Adventist Health Study.¹⁴ Koepsell et al.¹⁵ and Doody et al.¹⁶ reported population-based case-control data. Other reports come from hospital case-control studies.^{17–22}

Prospective studies have found an association of multiple myeloma with specific medical conditions. Isomaki et al. found twice the expected incidence of multiple myeloma in a rheumatoid arthritis cohort.¹³ The relative risk of myeloma after a history of any allergy in the Adventist Health cohort was 1.7. However, this was not a statistically significant increase.¹⁴

McWhorter examined the incidence of combined lymphoma, leukemia, and myeloma in a subset of the same NHANES I cohort used in the current study. He found an increased incidence of these neoplasms among patients who had a history of allergy.²³ McWhorter's data involves follow-up up to 1984 only and is limited to an examination of allergies as a risk factor. The risk of myeloma is not reported separately, presumably because only a small number of cases had occurred at the first wave of follow-up.

Two population-based case-control studies provide little support to an etiologic role of chronic anti-

genic stimulation. Koepsell et al., using cases from the Surveillance, Epidemiology, and End Results Reporting system and population-representative controls, found little support for the hypothesis.¹⁵ Of many potential risk factors, associations with fever blisters, urinary tract infections, and rheumatic fever were found. Doody et al. concluded that their data from a Kaiser Permanente cohort did not support a role for chronic antigenic stimulation in the etiology of hematopoietic malignancies. They did, however, find an elevated risk of myeloma with a history of eczema or musculoskeletal condition.¹⁶

Boffetta et al. reported a case-control study nested within the American Cancer Society prospective cohort. They found an association of myeloma only with diabetes among eight conditions examined. Although these exposure data were collected before disease development, the cohort consisted of volunteers who may have been self-selected into the study according to perceived health status.²⁴

Hospital-based case-control studies have given limited support to the antigenic stimulation hypothesis.¹⁷⁻²² However, because of the selection phenomenon known as Berkson bias,²⁵ hospital-based case-control studies are unsuitable for assessing an association with preexisting medical conditions. If the presence of multiple clinical conditions increases the probability of hospital admission, the hospital-based control group will have a higher prevalence of concurrent disease conditions than the background population. As a result of this selection process, a true association of multiple myeloma with other conditions may be masked in a hospital-based case-control study.

In the current analysis of data from the NHANES I cohort, we found evidence of increased risk of multiple myeloma among persons who reported at baseline interview that they had suffered from autoimmune or inflammatory conditions. The primary strength of the data results from their prospective nature. Data collected for a prospective cohort avoid the problems of selection bias associated with hospital-based case-control studies. They also avoid biased recall by the patient and interviewer bias, which can occur when a patient with a known condition is interviewed.

These findings are not conclusive. The results are based on only 18 multiple myeloma cases. Because the actual date of diagnosis was unavailable, the date of hospitalization or, for one case, date of death was substituted. The risk factor categories had to be constructed from the data that had been collected at the baseline interview. Therefore, the disease conditions that were included in the analysis are not a definitive list of diseases in each category.

Because the baseline data were collected for another purpose, a single questionnaire item could combine conditions with differing etiologies. For example, although only rheumatoid arthritis is thought to have an autoimmune component, the NHANES I item would include rheumatoid and osteoarthritis. The questionnaire item "arthritis" was included in the autoimmune category on the assumption that osteoarthritis would be randomly distributed between cases and controls and that, if an association was seen, it would be due to rheumatoid arthritis. Chronic or recurrent enteritis was thought to represent Crohn disease. Thyroid disease may represent Graves disease or other autoimmune thyroiditis. Both persons with multiple myeloma who reported thyroid disease also reported taking regular thyroid medication. Assumptions of this nature, which may result in misclassification of exposure, introduce a conservative bias by weakening the ability of the study to detect true associations.

Ten percent of patients with multiple myeloma may exhibit primary amyloidosis, which can manifest as amyloid induced arthritis or carpal tunnel syndrome.²⁶ When we limited the data analysis to persons who developed disease 5 or more years after the baseline interview, the association with autoimmune conditions disappeared. This suggests that the elevated relative risk found for autoimmune conditions present at the interview may be a spurious result of early disease symptoms.

Increased multiple myeloma risk was associated initially with higher educational levels.²⁷ These early findings may have been an artifact of under-diagnosed disease in less-educated persons.^{28,29} In the current study, persons with less than a high school education had a 6.6 times increased risk of multiple myeloma compared with persons with at least a high school education. Koepsell et al. and Boffetta et al. also reported an increased risk of myeloma at lower educational levels.^{15,24}

The biologic mechanism linking lower educational status with increased myeloma risk remains unclear. Myeloma has been associated with several occupational and chemical exposures.^{17,19,21,24} These may be more common among persons with less education and may explain part of this association.

Boice et al. have recently reported an increasing risk of multiple myeloma associated with increasing numbers of diagnostic radiographs.³⁰ Persons at the highest exposure level (a mean of 35 diagnostic radiographs) had relative risks of approximately four for multiple myeloma. Radiographs are used in the differential diagnosis of virtually all inflammatory conditions and many autoimmune conditions. Confounding by diag-

nostic radiographs could explain part of the association with immune-stimulating conditions seen in the current study, and the reverse might also be true. Additional studies should be designed to delineate the possible independent contributions of antigenic conditions and diagnostic radiographs to the etiology of multiple myeloma.

Clearly, all human beings are exposed to many antigens daily. Some of the medical conditions included in the current study are quite common. Persons who develop multiple myeloma may be characterized by a unique response to common exposures. The data of Leech and colleagues,³¹ who reported an excess of human leukocyte antigen-Cw5 among black patients with myeloma, and the numerous reports of family aggregation of multiple myeloma³² suggest that genetics play a role in increased risk. However, it will be a challenge to determine if genetic characteristics of the individual, environmental exposures, or behavioral factors interact with relatively common antigenic stimulation to place the individual at risk.

The data reported here, drawn from a nationally representative prospective study, show an association of inflammatory conditions with multiple myeloma. Inflammatory conditions show a dose-response relationship with number of conditions and time since initial inflammatory condition. These findings give limited support to the role of chronic stimulation of the immune system in the etiology of multiple myeloma. Because only a small number of myeloma cases were present in the cohort, the data lack the power to detect weak associations. Consequently, although there were no consistent associations of allergic, autoimmune, or chronic bacterial conditions with multiple myeloma, no conclusions about those risk factors can be drawn based on these data.

References

1. Salmon SE, Cassady JR. Plasma cell neoplasms In: DeVita VT, Hellman S, Rosenberg SA, editors. *Cancer: principles and practice of oncology*. Philadelphia: JB Lippincott, 1989:1853-89.
2. Bergsagel DE. Plasma cell myeloma: biology and treatment. *Annu Rev Med* 1991; 42:167-78.
3. Osserman EF, Takatsuki K. Considerations regarding the pathogenesis of the plasmacytic dyscrasias. *Series Haematologica* 1965; 4:28-49.
4. Goldenberg GJ, Paraskevas F, Israels LG. The association of rheumatoid arthritis with plasma cell and lymphocytic neoplasms. *Arthritis Rheum* 1969; 12:569-76.
5. Isobe T, Osserman EF. Pathologic conditions associated with plasma cell dyscrasias: a study of 806 cases. *Ann NY Acad Sci* 1971; 190:507-17.
6. Miller HW. Plan and operation of the Health and Nutrition Examination Survey, United States, 1971-1973. National Center for Health Statistics. *Vital Health Stat* (10a). Washington, DC: U.S. Government Printing Office, 1978.
7. Engel A, Murphy RS, Maurer K, Collins E. Plan and operation of the NHANES I Augmentation Survey of adults 25-74 years, United States, 1974-1975. National Center for Health Statistics. *Vital Health Stat* 1(14). Washington, DC: U.S. Government Printing Office, 1978.
8. Cohen BB, Barbano HE, Cox CS, Feldman JJ, Fincane FF, Kleinman JC, et al. Plan and operation of the NHANES I Epidemiologic Followup Study, 1982-84. *Vital and Health Statistics, Series 1*, No. 22, DHHS Pub. No. (PHS)87-1324, Public Health Service. Washington, DC: U.S. Government Printing Office, 1987.
9. Finucane FF, Freid VM, Madans JH, Cox CS, Kleinman JC, Rothwell ST, et al. Plan and operation of the NHANES I Epidemiologic Followup Study, 1986. National Center for Health Statistics. *Vital Health Stat* 1(25). Washington, DC: U.S. Government Printing Office, 1990.
10. Anderson S, Auquier A, Hauck WW, Oakes D, Vandaele W, Weisberg HI. *Statistical methods for comparative studies*. New York: John Wiley & Sons, 1980.
11. Harrell F. The PHGLM procedure. In: SAS supplemental library users guide. Cary, NC: SAS Institute, Inc., 1980:119-31.
12. Madans JH, Kleinman JC, Cox CS, Barbano HE, Feldman JJ, Cohen B, et al. Ten years after NHANES I: report of initial followup, 1982-84. *Public Health Rep* 1986; 101:465-73.
13. Isomaki HA, Hakulinen T, Joutsenlahti U. Excess risk of lymphomas, leukemia and myeloma in patients with rheumatoid arthritis. *J Chron Dis* 1978; 31:691-6.
14. Mills PK, Beeson L, Fraser GE, Phillips RL. Allergy and cancer: organ site-specific results from the Adventist health study. *Am J Epidemiol* 1992; 136:287-95.
15. Koepsell TD, Daling JR, Weiss NS, Taylor JW, Olshan AF, Lyon JL, et al. Antigenic stimulation and the occurrence of multiple myeloma. *Am J Epidemiol* 1987; 126:1051-62.
16. Doody MM, Linet MS, Glass AG, Freidman GD, Pottern LM, Boice JD, et al. Leukemia, lymphoma, and multiple myeloma following selected medical conditions. *Cancer Causes Control* 1992; 3:449-56.
17. Gallagher RP, Spinelli JJ, Elwood JM, Skippen DH. Allergies and agricultural exposure as risk factors for multiple myeloma. *Br J Cancer* 1983; 48:853-57.
18. Cohen HJ, Bernstein RJ, Grufferman S. Role of immune stimulation in the etiology of multiple myeloma: a case control study. *Am J Hematol* 1987; 24:119-26.
19. Linet MS, Harlow SD, McLaughlin JK. A case-control study of multiple myeloma in whites: chronic antigenic stimulation, occupation, and drug use. *Cancer Res* 1987; 47:2978-81.
20. Cuzick J, DeStavola B. Multiple myeloma: a case-control study. *Br J Cancer* 1988; 57:516-20.
21. Cuzick J, DeStavola BL. Autoimmune disorders and multiple myeloma [letter]. *Int J Epidemiol* 1988; 18:283.
22. Gramenzi A, Buttino I, D'Avanzo B, Negri E, Franceschi S, LaVecchia C. Medical history and the risk of multiple myeloma. *Br J Cancer* 1991; 63:769-72.
23. McWhorter WP. Allergy and risk of cancer: a prospective study using NHANES I followup data. *Cancer* 1988; 62:451-5.
24. Boffetta P, Stellman SD, Garfinkel L. A case-control study of multiple myeloma nested in the American Cancer Society prospective study. *Int J Cancer* 1989; 43:554-9.
25. Sackett DL. Bias in analytic research. *J Chron Dis* 1979; 32:51-63.
26. Schrier SL. Plasma cell myeloma and related serum protein disorders. In: Rubenstein E, Federman DD, editors. *Scientific American medicine*. New York: Scientific American, Inc., 1990:IX:5.

27. Hoover R, Mason TJ, McKay FW, Fraumeni JF. Geographic patterns of cancer mortality in the United States. In: Fraumeni JF, editor. *Persons at high risk of cancer*. New York: Academic Press, 1975:343-71.
28. Velez R, Beral V, Cuzick J. Increasing trends of multiple myeloma mortality in England and Wales, 1950-79: are the changes real? *J Natl Cancer Inst* 1982; 69:387-92.
29. Johnson JM, Grufferman S, Bourguet CC, Delzell E, DeLong ER, Cohen HJ. Socioeconomic status and risk of multiple myeloma. *J Epidemiol Community Health* 1985; 39:175-8.
30. Boice JD, Morin MM, Glass AG, Freidman GD, Stovall M, Hoover RN, et al. Diagnostic X-ray procedures and risk of leukemia, lymphoma, and multiple myeloma. *JAMA* 1991; 265:1290-4.
31. Leech SH, Bryan CF, Elston RC, Rainey J, Bickers JN, Pelias MZ. Genetic studies in multiple myeloma: 1. association with HLA-Cw5. *Cancer* 1983; 51:1408-11.
32. Olshan AF. Familial and genetic associations. In: Ostrom G, Potter M, editors. *Epidemiology and biology of multiple myeloma*. Berlin: Springer-Verlag, 1991:31-9.

Appendix

The following questions from the First National Health and Nutrition Survey were used to construct the categories of immune-stimulating conditions.

I. Allergies

Has a doctor ever told you that you have any of the following conditions and, if so, do you still have it? How many years ago did you first have it? Asthma, hives, hay fever, allergies to food, other allergies.

During the past 6 months, have you used any medicine, drugs, or pills for any of the following? Allergies, skin conditions.

Are you on a special diet? What is the diet for? Response— allergies. Was this diet ordered by a doctor? Response—yes.

II. Autoimmune Conditions

Has a doctor ever told you that you have any of the following conditions and, if so, do you still have it?

How many years ago did you first have it? Arthritis, rheumatic fever, diabetes, thyroid disease.

During the past 6 months, have you used any medicine, drugs, or pills for any of the following? Response—thyroid trouble.

Are you on a special diet? What is the diet for? Response— diabetes. Was this diet ordered by a doctor? Response—yes.

Did a doctor ever tell you that you had protein, albumin, blood, or sugar in your urine? Which? Response—sugar.

Pernicious anemia: Did a doctor tell you that you had anemia? What caused it? Response—illness. Were you treated for this condition by a doctor? Response—yes. Was the treatment vitamin shots? Are you still being treated for it? Response—yes.

III. Chronic Bacterial Infections

Has a doctor ever told you that you have any of the following conditions and, if so, do you still have it? How many years ago did you first have it? Chronic bronchitis or emphysema; chronic cough; tuberculosis; peptic, stomach, or duodenal ulcer.

During the past 6 months have you used any medicine, drugs, or pills for any of the following? Response—infection.

Are you on a special diet? What is the diet for? Response—ulcers. Was this diet ordered by a doctor? Response—yes.

Have you ever had an abdominal operation? What was it for? Response—ulcers.

IV. Inflammatory Conditions

Has a doctor ever told you that you have any of the following conditions and, if so, do you still have it? How many years ago did you first have it? Gout, gallstones, recurrent or chronic enteritis, pleurisy.

Have you ever had an abdominal operation? What was it for? Response—gallstones.