

Multiple Myeloma and Family History of Cancer among Blacks and Whites in the U.S.

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BACKGROUND. In the U.S., the incidence rate of multiple myeloma is more than twice as high for blacks as for whites, but the etiology of this malignancy is not well understood.

METHODS. A population-based case-control interview study of 565 subjects (361 white, 204 black) with multiple myeloma and 2104 controls (1150 white, 954 black) living in 3 areas of the U.S. offered the opportunity to explore whether family history of cancer contributes to the risk of multiple myeloma and explains the racial disparity in risk.

RESULTS. For both races combined, the risk of multiple myeloma was significantly elevated for subjects who reported that a first-degree relative had multiple myeloma (odds ratio [OR] = 3.7, 95% confidence interval [CI] = 1.2–12.0). Increased risk was also associated with a family history of any hematolymphoproliferative (HLP) cancer (OR = 1.7, 95% CI = 1.0–2.8), especially in a sibling (OR = 2.3, 95% CI = 1.1–4.5). The risk associated with familial occurrence of HLP cancer was higher for blacks than for whites, but the difference between the ORs was not statistically significant.

CONCLUSIONS. These data are consistent with previous studies that indicate a familial risk of multiple myeloma, but they explain little of the race-related difference in incidence rates. *Cancer* 1999;85:2385–90.

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In the U.S., the incidence rate of multiple myeloma, a B-cell malignancy, is twice as high for blacks (9.5 per 100,000) as for whites (4.1 per 100,000).¹ To investigate postulated risk factors for this cancer² and reasons for the race-related difference, we conducted a population-based case-control study of blacks and whites in three geographic regions of the U.S. A prior study of a subset of male subjects who provided a blood sample revealed an association between multiple myeloma and the HLA-Cw2 allele.³ Although the frequency of the allele was greater among black patients than among white patients, it was present at about the same frequency in black and white controls, suggesting that Cw2 may contribute only in part to the higher incidence of multiple myeloma among blacks. Familial cancer history has been evaluated in a few epidemiologic studies of multiple myeloma,^{4–6} but none have examined risks separately among whites and blacks. In this study, we evaluated the relation between familial cancer history and risk of multiple myeloma, and its possible effect on the race-related difference in the incidence rate of multiple myeloma in the U.S.

METHODS

Cases and Controls

This population-based case-control interview study of multiple myeloma, conducted during the years 1986-1989, was one component of a multicenter study of four types of cancer (multiple myeloma, esophagus, pancreas, and prostate) that occur more frequently among blacks than among whites. For efficiency, one large general-population control group was included for all four cancer types. Subjects were residents of geographic areas covered by 3 population-based cancer registries: the Georgia Center for Cancer Statistics (DeKalb and Fulton counties), the Metropolitan Detroit Cancer Surveillance System (Macomb, Oakland, and Wayne counties), and the New Jersey State Cancer Registry (10 counties).

Eligible cases were all white and black residents ages 30-79 years who were newly diagnosed with multiple myeloma (as reported in pathology, hematology, outpatient, or tumor registry records at hospitals in the 3 areas) between August 1, 1986, and April 30, 1989. Efforts to verify diagnoses by assessing the percentage of plasma cells or other manifestations of disease were beyond the scope of the current investigation, as was a detailed review of all hospital and laboratory records to ascertain all patients with monoclonal gammopathy of undetermined significance (MGUS). To reduce the proportion of deceased patients at the time of interview, efforts were made to ascertain and interview patients within 3 months of diagnosis. Of the 581 white and 309 black cases of multiple myeloma ascertained, interviews were conducted with 367 whites (63%) and 208 blacks (67%). Nonresponse included death (21% for both races), illness (whites 7%, blacks 6%), or refusal to be interviewed (whites 8%, blacks 5%).

Controls were frequency matched to the age, race, gender, and area distribution of cases with all four types of cancer combined. For each geographic area, registry data from prior years were used to estimate the race-, gender-, and age-specific (5-year age groups) numbers of cases expected to construct a sampling frame for controls. Controls were selected from two sources. Random-digit dialing (RDD) techniques⁷ were used to select controls ages 30-64 years, with telephone coverage for our study areas estimated as greater than 90%.⁸ Computerized listings of Medicare recipients provided by the Health Care Financing Administration (HCFA), stratified by age, gender, and race, were used to select systematically (after a random start) controls ages 65-79 years. Among controls, interviews were conducted with 1227 (78% of both whites and blacks) of the 1568 eligible subjects from

RDD and 926 (75%) of the 1232 persons selected from HCFA files. The interview response rates for the HCFA controls were 73% for whites and 78% for blacks. Because the response rate for the household screening phase for the RDD controls was 86%, the overall participation rate for RDD controls was 67%. Among eligible controls, refusal to be interviewed was the most common reason for nonresponse (whites 17%, blacks 13%), followed by illness or death (whites 3%, blacks 4%) and other problems (whites 3%, blacks 4%).

Excluded from the analysis were 2 cases and 7 controls with unreliable questionnaire responses as assessed by the interviewer, 15 white controls ages 30-34 years because there were no comparably aged white cases, and 8 cases and 27 controls who did not respond to the question about family history of cancer. The final study group for this analysis consisted of 361 white cases (189 male, 172 female), 204 black cases (89 male, 115 female), 1150 white controls (732 male, 418 female), and 954 black controls (603 male, 351 female). Further details of case-control selection have been published elsewhere.⁹

Data Collection

In-person interviews were conducted with the cases and controls by trained interviewers, usually in the subject's home. Informed consent to participate in the study was obtained from each subject prior to interview. Detailed information was obtained regarding several factors possibly related to multiple myeloma, including family history of cancer, use of alcohol and tobacco, usual adult diet, lifetime occupation, medical history, and sociodemographic factors.

The objective of the familial component of this study was to ascertain the risk of multiple myeloma, as estimated by the odds ratio (OR), in association with a reported history of multiple myeloma, any hematolymphoproliferative (HLP) cancer (defined as multiple myeloma, leukemia, or lymphoma), other HLP cancer (defined as leukemia or lymphoma, but not multiple myeloma), non-HLP cancer, any type of cancer, and selected common cancers (prostate, lung, breast, and colon) among the first-degree relatives (parents, siblings, children) of cases and controls. To ascertain family history of cancer, subjects were asked, "Were any of your immediate blood relatives, including your mother, father, brothers, sisters, sons, or daughters, ever diagnosed as having a malignant tumor, leukemia, Hodgkin disease, or any other type of cancer?" If yes, they were asked, "Who was diagnosed as having cancer, that is, what was his or her relationship to you?" and "What type of cancer did your [relative] have, or in what part of the body did the cancer start?" Risk associated with a history of cancer occur-

TABLE 1
Risk of Multiple Myeloma by Race According to Family History of Hematolymphoproliferative Cancer (HLP)^a

	White ^b				Black ^b				Total ^c			
	Case n	Control n	OR	95% CI	Case n	Control n	OR	95% CI	Case n	Control n	OR	95% CI
No family history	182	646	1.0	—	142	679	1.0	—	324	1325	1.0	—
Any first-degree relative												
Any HLP	13	32	1.3	0.6–2.5	9	18	2.2	0.9–5.1	22	50	1.7	1.0–2.8
Multiple Myeloma	3	5	1.5	0.3–6.4	4	1	17.4	2.4–348	7	6	3.7	1.2–2.0
Other HLP ^d	10	27	1.2	0.6–2.6	5	17	1.3	0.4–3.5	15	44	1.3	0.7–2.4
Any Non-HLP	158	453	1.2	0.9–1.6	47	239	0.8	0.6–1.2	205	692	1.1	0.9–1.3
Any parent												
Any HLP	8	27	1.0	0.4–2.1	6	11	2.5	0.8–7.0	14	38	1.4	0.7–2.6
Any non-HLP	101	323	1.2	0.9–1.6	23	145	0.7	0.4–1.1	124	468	1.0	0.8–1.2
Any sibling												
Any HLP	9	14	1.8	0.7–4.5	6	9	2.6	0.8–7.7	15	23	2.3	1.1–4.5
Any non-HLP	78	182	1.3	0.9–1.8	27	114	1.0	0.6–1.6	105	296	1.2	0.9–1.6

OR: odds ratio; CI: confidence interval.

^a All OR relative to risk of 1.0 for subjects with no family history of cancer.^b All OR adjusted for age, study area, and gender.^c All OR adjusted for age, study area, gender, and race.^d Includes relatives with leukemia and lymphoma but not multiple myeloma.

ring in the children of subjects was not assessed separately, as the number of subjects who reported children with cancer was small.

Data Analysis

Unconditional logistic regression models¹⁰ using the SAS Logistic Procedure¹¹ were used to obtain maximum likelihood estimates of adjusted odds ratios (OR) and approximate 95% confidence intervals (CIs) for the family cancer history variables of interest. ORs were adjusted for the selection factors: age at interview (30–34 years, 35–39, and so on, up to 75–79), geographic area (Atlanta, Detroit, New Jersey), race (black, white), and gender (male, female). Both race-adjusted and race-specific ORs are presented in the tables. In a previous report based on these data, we indicated that alcohol and tobacco intake were not related to risk of multiple myeloma.¹² Several potential confounders were evaluated, including education, marital status, income, and socioeconomic status, but were not included in the final logistic model because they did not confound the relation between family cancer history and the risk of multiple myeloma. Population-attributable risk estimates of the proportion of multiple myeloma due to familial multiple myeloma and the estimated annual incidence rates for those with and without a family history of multiple myeloma were not calculated because the small number of familial multiple myelomas would generate unstable estimates.

RESULTS

As shown in Table 1, family history of an HLP cancer in a first-degree relative was reported by 22 cases (3.9% overall, 3.6% in whites, and 4.4% in blacks) and 50 controls (2.4% overall, 2.8% in whites, and 1.9% in blacks), yielding an adjusted OR of 1.7 (95% CI = 1.0–2.8). Risk of multiple myeloma was lower for whites (OR = 1.3, 95% CI = 0.6–2.5) than for blacks (OR = 2.2, 95% CI = 0.9–5.1) who reported any relative with a history of HLP malignancy. In contrast, we found no excess risk for non-HLP cancer (OR = 1.1, 95% CI = 0.9–1.3). Risks were greater for subjects with HLP cancer in siblings (OR = 2.3, 95% CI = 1.1–4.5) than for those with HLP cancer in parents (OR = 1.4, 95% CI = 0.7–2.6), but the ORs were not significantly different. Risks associated with a family history of HLP cancer were elevated in both males (OR = 1.8, 95% CI = 0.8–3.7) and females (OR = 1.4, 95% CI = 0.6–2.9) and in those age 60 years or older (OR = 2.0, 95% CI = 1.1–3.6), but not in those younger than 60 years (OR = 0.9, 95% CI = 0.2–2.7). Two black male cases and one white female control reported having more than one first-degree relative with a history of HLP cancer. Both cases reported a mother with multiple myeloma, whereas one case also reported a brother and the other a sister with leukemia. The control reported both a mother and a sister with leukemia.

The risk associated with a family history of multi-

TABLE 2
Risk of Multiple Myeloma by Race According to Family History of Selected Cancers^a

	White ^b				Black ^b				Total ^c			
	Case n	Control n	OR	95% CI	Case n	Control n	OR	95% CI	Case n	Control n	OR	95% CI
No family history	182	646	1.0	—	142	679	1.0	—	324	1325	1.0	—
Cancer type												
Any	179	504	1.2	1.0–1.6	62	275	1.0	0.7–1.4	241	779	1.1	0.9–1.4
Prostate	17	34	1.7	0.9–3.2	3	14	1.0	0.2–3.2	20	48	1.4	0.8–2.5
Lung	32	77	1.5	0.9–2.4	9	35	1.1	0.5–2.4	41	112	1.4	0.9–2.0
Breast	29	75	1.1	0.7–1.9	9	49	0.7	0.3–1.5	38	124	1.0	0.7–1.5
Colon	13	53	0.9	0.4–1.6	5	19	1.1	0.3–2.8	18	72	0.9	0.5–1.5

OR: odds ratio; CI: confidence interval.

^a All OR relative to risk of 1.0 for subjects with no family history of cancer.

^b All OR adjusted for age, study area, and gender.

^c All OR adjusted for age, study area, gender, and race.

ple myeloma (OR = 3.7, 95% CI = 1.2–12.0) was higher than the risk associated with a family history of other HLP cancer (OR = 1.3, 95% CI = 0.7–2.4). Although based on small numbers, the risks were much greater for blacks (OR = 17.4, 95% CI = 2.4–348) than for whites (OR = 1.5, 95% CI = 0.3–6.4). Risks associated with a family history of leukemia or lymphoma were 1.7 (95% CI = 0.9–3.1) and 0.7 (95% CI = 0.0–4.0), respectively (data not shown). None of the subset of 25 male cases with the HLA-Cw2 allele reported a familial occurrence of multiple myeloma or other HLP cancer.

Table 2 presents the risks of multiple myeloma associated with a family history of any cancer and four common non-HLP adult cancers (prostate, lung, breast, and colon). Small, nonsignificant elevated risks were seen for both races combined among persons who reported carcinoma of the prostate or lung, but not breast or colon carcinoma, in a first-degree relative. The excess risk among those with a family history of prostate or lung carcinoma was present only in whites (OR = 1.7 and 1.5, respectively).

DISCUSSION

To our knowledge, our population-based, case-control interview study was the first to evaluate the risks of multiple myeloma among large numbers of whites and blacks in relation to a family history of HLP and other cancers. Overall, we found an almost fourfold excess risk among subjects who reported having a first-degree relative with multiple myeloma. This elevated risk fell between the ORs of 2.3 (95% CI = 0.5–10.1) and 5.6 (95% CI = 1.2–27.5) reported in 2 previous case-control studies that evaluated the familial risks of multiple myeloma.^{4,6} Our estimate of

familial risk was substantially higher for blacks than for whites, but the ORs were based on a small number of affected first-degree relatives. Therefore, even if the familial predisposition to multiple myeloma were greater among blacks than whites, it would explain only a small part of the higher incidence in the black U.S. population. The amount of multiple myeloma due to family history in both races would be small because the prevalence of familial multiple myeloma in the general population is low.

The risk of multiple myeloma associated with any familial HLP cancer was also increased, especially among those reporting an affected sibling. The risk estimates tended to be higher among blacks than among whites, but they were not significantly different from each other. Our findings are consistent with clinical and epidemiologic observations suggesting that multiple myeloma tends to arise in families with leukemia or lymphoma.^{4–6,13,14}

The familial tendency toward development of multiple myeloma in our study, together with our prior study implicating the HLA-Cw2 allele in multiple myeloma,³ suggest that genetic susceptibility contributes to the origins of this neoplasm, although shared environmental risk factors may be involved as well. We found elevated risks of multiple myeloma in both races combined, ranging from 1.4 to 1.7, associated with low levels of education, income, and socioeconomic status, and recent studies have suggested that viruses may be involved in the etiology of multiple myeloma.¹⁵ Innovative study designs would be required to disentangle the influence of genetic factors from shared environmental factors affecting the familial risk of multiple myeloma.

A possible genetic marker is the B-allele polymor-

phism of the poly(ADP-ribose) polymerase tumor suppressor gene located on the long arm of chromosome 13. The frequency with which this polymorphism occurs is increased in patients with multiple myeloma and the precursor state of monoclonal gammopathy,¹⁶ and it is also expressed more frequently in blacks (35%) than in whites (14%) in the population.¹⁷ A heritable component may extend not only to other HLP cancers, but also to solid tumors, as suggested by a possible excess of multiple myeloma reported among first-degree relatives of carriers of the BRCA1 or BRCA2 mutations.¹⁸ In our study, we observed a modest excess risk of multiple myeloma in subjects whose first-degree relatives had prostate carcinoma (whites only), whereas no relation was seen for breast carcinoma. The tendency for prostate carcinoma and multiple myeloma to aggregate in families has been suggested in other case-control studies,^{6,19} although the findings have not been conclusive.

The strengths of our study include the use of a large, population-based incident series of blacks and whites newly diagnosed with multiple myeloma; in-person interviews conducted directly with all study subjects generally within 6 months of diagnosis; quantitative estimates based on cancers reported in first-degree relatives only; and exclusion of all respondents judged to be unreliable, thus enhancing the accuracy of risk estimates. There are, however, several limitations of our study, including the use of in-person interviews for collecting family cancer history without validation; lack of systematic identification of all first-degree relatives, their birth dates, and their ages at cancer diagnosis; possible biases resulting from relatively low response rates, the tendency to interview cases with better survival, the potential for heightened recall of cases versus controls and of differential reporting of family history by race; and the play of chance that may explain associations based on small numbers. In addition, the small number of familial multiple myelomas in this and other studies made it difficult to obtain precise estimates of risk and thus to compare adequately ORs between blacks and whites.

In summary, the results of our population-based case-control study of blacks and whites in the U.S. are consistent with a familial risk of multiple myeloma, although family history of multiple myeloma or other HLP cancer explains little of the race-related difference in incidence rates. The race-related difference in familial risks may actually be smaller than reported herein if our results were influenced by underreporting of multiple myeloma and other HLP cancers among first-degree relatives of controls in conjunction with small numbers of

affected cases and controls. Additional large studies of racially diverse populations (ideally with complete ascertainment of multiple myeloma and other HLP cancers among close relatives) are needed to generate adequate numbers of familial cases to clarify the genetic mechanisms and gene-environment interactions that may contribute to familial and racial susceptibility to multiple myeloma.

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