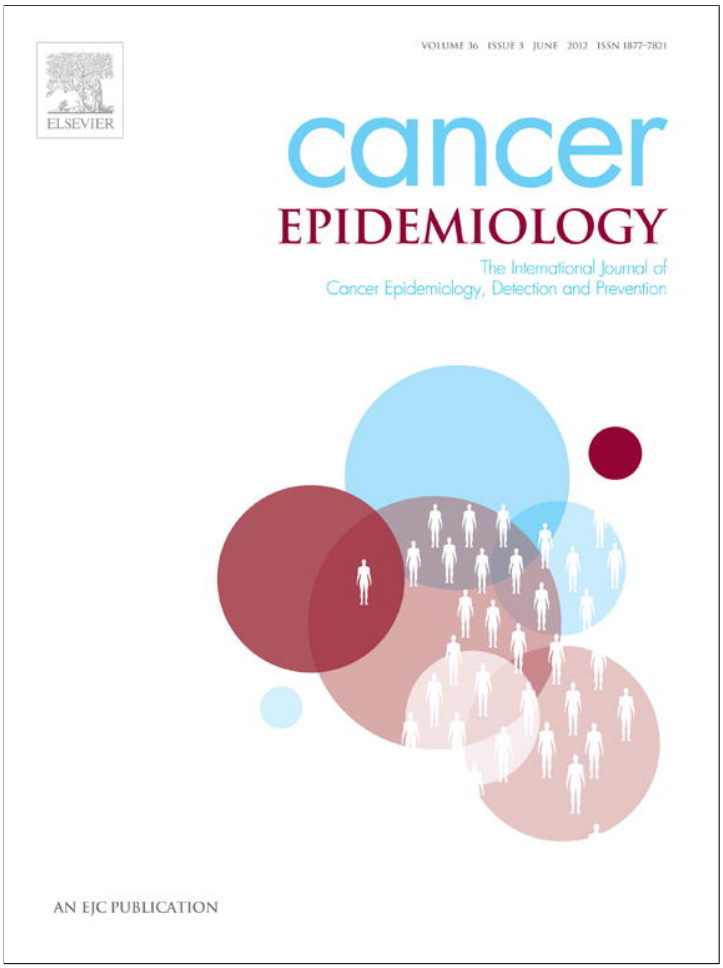

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Short communication

Family history of non-hematologic cancers among Waldenstrom macroglobulinemia patients: A preliminary study

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ABSTRACT

Background: Little is known about the epidemiology and etiology of Waldenstrom macroglobulinemia (WM). Despite several studies of the relation between family history and B-cell disorders and WM, family history of non-hematologic cancers has not been systematically investigated. We thus examined associations of family history of breast, colorectal, lung, ovarian, and prostate cancers with WM.
Methods: All probands aged 20–79 years with bone marrow biopsy-confirmed diagnosis of WM between May 1, 1999 and January 1, 2010 at the Bing Center for Waldenstrom Macroglobulinemia were eligible for inclusion in our analysis. We reviewed medical records for eligible probands to determine family history of cancer (defined as a cancer diagnosis for ≥1 first-degree relative(s) of the proband). Using expected values constructed from the United States National Health Interview Survey, we estimated age- and race-standardized rate ratios (RRs) for family history of breast, colorectal, lung, ovarian, and prostate cancers by WM subtype.
Results: Family history of prostate cancer had the largest overall rate ratio (RR = 1.4, 95% confidence limits [CL]: 1.1, 1.7), and among sporadic cases, family history of prostate and breast cancer had the largest rate ratios (prostate: RR = 1.3, 95% CL: 1.1, 1.7; breast: RR = 1.3, 95% CL: 1.2, 1.6).
Conclusion: Our study suggests that it may be worthwhile to pursue these associations in a case–control study with uniform selection and data collection for cases and controls, and at least some record-based information on family history.

1. Introduction

Waldenstrom Macroglobulinemia (WM) is a distinct subtype of B-cell non-Hodgkin lymphoma predominantly diagnosed among older adults. WM patients typically present with symptoms related to bone marrow infiltration of lymphoplasmacytic cells and manifestation of an immunoglobulin *M* (IgM) monoclonal gammopathy, but a sizable proportion of patients may be asymptomatic [1]. Although the proportion of undiagnosed cases is unknown, the estimated annual incidence rate of WM after age 65 in the United States is 3.7/100,000 [2], with a similar incidence rate in England [3]. Nonetheless, age, sex, and race are currently the only established risk factors [4].

Studies of familial aggregation have long been used for generating hypotheses regarding shared genetic and environmental factors [5,6]. Previous studies suggest that genetic and environmental risk factors for B-cell disorders may also be risk factors for WM [7–9], but additional hypothesis sources are needed. We thus examined potential associations of WM with

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family history of non-hematologic malignancies overall and by WM subtypes.

2. Patients and methods

2.1. Study population

We used data from consecutive WM probands evaluated at the Bing Center for Waldenstrom's Macroglobulinemia located at Dana-Farber Cancer Institute. This study population comprises referrals for the evaluation and management of WM. To improve comparability between these cases and the National Health Interview Survey (NHIS) data used to ascertain exposure prevalence among controls [10], we restricted probands to be aged 20–79 years with bone marrow biopsy-confirmed diagnosis of WM between May 1, 1999 and January 1, 2010. The study was approved by the Dana-Farber Cancer Institute/Harvard Cancer Center Institutional Review Board.

2.2. Data collection and variables

Family histories of cancers were ascertained by self-report during intake interviews by healthcare professionals who inquired whether first-degree blood relatives (biologic parents, siblings, or children) of the proband ever had cancer and, if so, the type. This information was recorded in medical records for each proband as part of standard clinical procedures for newly diagnosed WM patients. We reviewed medical records for eligible probands to determine family histories of hematologic, breast, colorectal, lung, ovarian, and prostate cancers. Family history of cancer was defined as a cancer diagnosis for $\geq$1 first-degree relative(s) of the proband; we had insufficient data to explore other definitions. Age at diagnosis of the primary cancer was not available for relatives.

Data regarding family history of cancer were used to classify probands according to WM subtypes: (1) familial WM: $\geq$1 relative diagnosed with WM or a related B-cell disorder (multiple myeloma, Burkitt lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, mucosa-associated lymphoid tissue [MALT] lymphoma, monoclonal gammopathy of undetermined significance [MGUS], chronic lymphocytic leukemia, or hairy cell leukemia); and (2) sporadic WM: no relative diagnosed with WM or related B-cell disorders. Medical records were also reviewed for the proband to collect data regarding age at diagnosis of WM, gender, and self-reported race (White, Black, or Other).

2.3. Data analysis

Our analysis involved comparing the age- and race-standardized exposure prevalence (family history of cancer) in a series of WM cases (overall and by WM subtype) to the exposure prevalence ascertained in the NHIS [10]. The NHIS is an annual health survey of the civilian noninstitutionalized United States population [10]. The 2000 NHIS included a Cancer Control Module in which participants were asked whether first-degree blood relatives ever had cancer and, if so, the type [10]. This approach allowed us to circumvent resource constraints on obtaining individual-level exposure data for a sample of the source population but still evaluate associations between family history of cancer and WM within a case–control framework [11, Ch. 8]. Briefly, if the exposure prevalence (p) in the source population for the cases is known and M cases are available for study, then $E = pM$ is the expected number of cases exposed under the null hypothesis of no association of exposure with selection or disease. Therefore, if A of the M cases are exposed, the rate ratio (RR) estimator is:

$$\mathrm{RR} = \frac{A/p}{(M-A)/(1-p)} = \frac{A/(M-A)}{E/(M-E)}$$

The age- and race-specific prevalence (p) of family history of breast, colorectal, lung, ovarian, and prostate cancers in the general US population was determined from published estimates [10]. Confidence limits (CL) for the rate ratio were calculated as RR·exp ($\pm 1.96 \cdot V$) where V is the ln(RR) variance estimate $1/A + 1/(M-A)$. This formula ignores sampling variability in E which, in the present setting, is much smaller than the variability in A. Gender was omitted from adjustment because it is effectively randomized at conception, making it unrelated to family history and thus incapable of confounding [11, Ch. 9, 12].

2.4. Sensitivity analysis

We explored the potential impact of misclassification of self-reported family history of prostate and breast cancers between cases and the general population in a sensitivity analysis using initial values suggested by published estimates of sensitivity (Se) and false-positive rate (Fp = 1 − specificity) for self-reported family history of cancer among lymphoma probands [12]. Adjusted case numbers were computed from:

$$A = \frac{A^* - \mathrm{Fp}_{\mathrm{cases}} M}{\mathrm{Se}_{\mathrm{cases}} - \mathrm{Fp}_{\mathrm{cases}}} \text{ and}$$

$$E = \frac{E^* - \mathrm{Fp}_{\mathrm{controls}} M}{\mathrm{Se}_{\mathrm{controls}} - \mathrm{Fp}_{\mathrm{controls}}}$$

where A^* and E^* are the original unadjusted numbers [11, Eq. 19–8].

3. Results

We identified 903 eligible probands but restricted the analysis to the 864 WM probands aged 20–79 years who were diagnosed with WM between May 1, 1999 and January 1, 2010, and had complete data. Table 1 summarizes characteristics of the WM probands. Briefly, the median age of WM diagnosis in our study population was 59 years (interquartile range = 52–65 years), 62% were male (n = 538), 97% were White (n = 835), and 15% (n = 101) of the 675 probands with detailed ethnicity information reported an Ashkenazi–Jewish background. Our case series comprised 73% sporadic WM cases (n = 631) and 27% familial WM cases (n = 233). The prevalence of family history of non-hematologic cancers ranged from 13% for breast to 2% for ovarian.

Table 2 summarizes rate ratio estimates for WM associated with family history of cancer, which ranged from RR = 1.4 (95% CL: 1.1, 1.7) for prostate to RR = 0.75 (95% CL: 0.46, 1.2) for ovarian. The estimates for sporadic cases were similar to the overall estimates. Among familial WM cases, the estimates ranged from RR = 1.5 (95% CL: 1.0, 2.2) for family history of prostate cancer to RR = 0.51 (95% CL: 0.32, 0.84) for family history of lung cancer.

Table 3 summarizes the adjusted RR for values of the sensitivity parameters, varied around the values reported by Chang et al. [12]. On average the adjustments did not notably influence estimates for the association between family history of breast cancer and WM regardless of whether nondifferential or differential misclassification was assumed. The adjusted estimates for the association between family history of prostate cancer and WM demonstrated greater sensitivity to assumptions of differential than nondifferential misclassification, and generally increased when the false-positive rate was assumed to be equivalent between WM cases and the NHIS population.

4. Discussion

We aimed to examine potential associations of WM with family history of non-hematologic malignancies overall and by WM

Table 1
Characteristics of 864 Waldenstrom Macroglobulinemia (WM) probands evaluated at the Bing Center for Waldenstrom's Macroglobulinemia between May 1, 1999 and January 1, 2010.

Characteristic	Familial WM ($n=233$)	Sporadic WM ($n=631$)	All WM cases ($n=864$)	NHIS population[b]
Age at WM diagnosis, median (IQR[a])	58 (51–63)	59 (52–66)	59.0 (52–65)	–
Male, *n* (%)	135 (58.0)	403 (63.9)	538 (62.3)	
Race, *n* (%)				–
White	226 (97.0)	609 (96.5)	835 (96.6)	–
Black	3 (1.3)	8 (1.3)	11 (1.3)	–
Other	4 (1.7)	14 (2.2)	18 (2.1)	–
Family history of cancer, *n* (%)				(%)
Breast	19 (8.2)	96 (15.2)	115 (13.3)	7.7
Colorectal	17 (7.3)	55 (8.7)	72 (8.3)	5.0
Lung	14 (6.0)	69 (10.9)	83 (9.6)	7.1
Ovarian	4 (1.7)	11 (1.7)	15 (1.7)	1.8
Prostate	23 (9.9)	56 (8.9)	79 (9.1)	4.7

[a] IQR: interquartile range.
[b] Prevalence estimates (p) ascertained from National Health Interview Survey (NHIS) [10].

Table 2
Estimated rate ratios (RR) relating family history of non-hematologic cancers to Waldenstrom Macroglobulinemia (WM) by WM subtype.

Family history	Familial WM[a] A/E[b]	Familial WM RR (95% CL[c])	Sporadic WM A/E	Sporadic WM RR (95% CL)	Overall WM A/E	Overall WM RR (95% CL)
Breast	19/27	0.67 (0.44, 1.0)	96/75	1.3 (1.2, 1.6)	115/103	1.1 (1.0, 1.3)
Colorectal	17/19	0.89 (0.57, 1.4)	55/52	1.1 (0.83, 1.4)	72/71	1.0 (0.82, 1.3)
Lung	14/26	0.51 (0.32, 0.84)	69/69	1.0 (0.81, 1.2)	83/95	0.86 (0.71, 1.0)
Ovarian	4/5	0.74 (0.28, 1.9)	11/15	0.75 (0.42, 1.3)	15/20	0.75 (0.46, 1.2)
Prostate	23/16	1.5 (1.0, 2.2)	56/43	1.3 (1.0, 1.7)	79/59	1.4 (1.1, 1.7)

[a] Familial WM defined as family history of B-cell disorders.
[b] A, number of exposed cases; M, total number of cases; $E = Mp$ = expected number of exposed cases based on NHIS, $RR = (A/p)/[(M-A)/(1-p)] = [A/(M-A)]/[E/(M-E)]$.
[c] CL: confidence limits.

subtypes. Our design cannot separate factors related to incidence from factors related to selection or information, a particular limitation given the case series is a referral group using clinical data whereas the controls are from population survey data. In particular, the WM cases in our analysis were from a specialized referral center and thus may not have histories representative of all WM cases from the source population. Of note, about 40% of the WM cases in our sample were asymptomatic, and the proportion of asymptomatic cases among all WM cases is unknown. While this problem may not have strongly biased our estimates, an additional problem is that the NHIS data [10] used to ascertain population prevalence of family history of cancers may not be representative of the source population of our cases. Any discrepancy not accounted for by our age-race adjustment would thus bias our estimates. Unfortunately, we lack additional information to evaluate this possible bias.

Another concern in our analysis is different exposure misclassification rates for cases and the NHIS population serving as controls. Recall bias in case–control studies is typically assumed to be a consequence of higher exposure misclassification among

Table 3
Rate ratios (RR) after adjustment for misclassification of self-reported family history of breast and prostate cancers.

	Scenario	Cases		NHIS population		Adjusted RR
		Sensitivity	False-positive	Sensitivity	False-positive	
Breast	1[a]	1.00	0	1.00	0	1.1
	2[b]	0.73	0.01	0.72	0.01	1.1
	3	0.85	0.01	0.72	0.01	1.0
	4	0.73	0.01	0.85	0.01	1.4
	5	0.73	0.05	0.72	0.05	1.2
	6	0.85	0.05	0.72	0.05	1.0
	7	0.73	0.05	0.85	0.05	1.5
	8	0.73	0.05	0.72	0.01	0.77
	9	0.85	0.05	0.72	0.01	0.64
	10	0.73	0.05	0.85	0.01	0.93
Prostate	1[a]	1.00	0	1.00	0	1.4
	2[b]	0.47	0.01	0.60	0.01	2.0
	3	0.47	0.01	0.47	0.01	1.5
	4	0.73	0.01	0.60	0.01	1.2
	5	0.47	0.05	0.60	0.05	3.2
	6	0.47	0.05	0.47	0.05	2.4
	7	0.73	0.05	0.60	0.05	1.9
	8	0.47	0.05	0.60	0.01	1.0
	9	0.47	0.05	0.47	0.01	0.76
	10	0.73	0.05	0.60	0.01	0.59

[a] Assumes no misclassification; equivalent to rate ratio estimated in study.
[b] Adjustment based on published estimates of sensitivity and false-positive rate for self-reported family history of cancer among lymphoma probands [12].

controls than cases, which could upward bias estimates. Nonetheless, a prior validation study [12] among lymphoma probands noted that misclassification of family history of cancer may be higher among cases than controls, which could result in a downward bias greater than that expected from nondifferential recall [13]. Our sensitivity analysis based on the lymphoma validation study reflected this finding, with generally stronger magnitudes of association between family history of prostate cancer and WM. Our sensitivity analysis is speculative, however, being limited by differences in exposure measurement between our study and the lymphoma study, and the fact that the lymphoma data are themselves subject to error.

Although our estimates are subject to differential selection and information effects, they suggest a modest association between family history of prostate cancer and WM incidence, and a similar association between family history of breast cancer and WM among sporadic cases. We used the common definition of family history of cancer (i.e. affected first-degree relatives), but other definitions (e.g. inclusion of affected 2nd degree relatives, young onset, etc. which could not be explored with our data) might yield different associations. The associations we observed appear to differ from associations reported in an analysis that aggregated non-Hodgkin lymphoma subtypes [14]. This discrepancy may provide additional evidence for etiologic heterogeneity among non-Hodgkin lymphoma subtypes suggested in a previous study [15].

Positive population associations for family history of prostate cancer and breast cancer with WM, particularly for probands with sporadic WM, would suggest shared genetic or environmental risk factors between breast and prostate cancer, and WM. For example, *BRCA* mutations are well-known risk factors for breast cancer [16] and have also been implicated in prostate cancer [17]. Recent evidence also indicates that normal *BRCA* functioning is critical for suppressing hematologic malignancies [18] and thus *BRCA* mutations may be relevant to WM. Therefore, we would encourage case–control studies specifically designed to explore the relation of family history of various cancers to WM which include uniform selection criteria for cases and controls, and a validation component that obtains measures of family history (e.g. reviews of medical records, vital records, etc.) that are free of differential error. These measurements can be used to generate improved estimates of association between family history and WM [11, Ch. 19].

Conflict of interest

The authors declare no competing financial or non-financial interests.

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