

Waldenström's Macroglobulinemia

Incidence Patterns in the United States, 1988–1994

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BACKGROUND. There are few data describing the epidemiologic aspects of Waldenström's macroglobulinemia (WM), a rare lymphoplasmaproliferative disorder.

METHODS. The authors evaluated the incidence of WM reported in 11 population-based cancer registries in the U.S.

RESULTS. A total of 624 cases were diagnosed between January 1, 1988 (when WM became reportable) and December 31, 1994. Age-adjusted incidence rates for WM (per 1 million person-years at risk) were 3.4 among males and 1.7 among females. The rates increased sharply with age, from 0.1 at age < 45 years to 36.3 at age 75+ years (males) and from 0.1 at age < 45 years to 16.4 at age 75+ years (females). The rates for WM were comparable to those for hairy cell leukemia, but considerably lower than those for multiple myeloma or chronic lymphocytic leukemia. Some geographic variation was evident, with age-adjusted rates among white males ranging from 2.2–7.8 across registries. There was no significant change in rates over the 7-year study period ($P > 0.05$). The markedly higher rates for WM among whites than blacks stand in contrast to multiple myeloma, which occurs twice as often among blacks.

CONCLUSIONS. This survey provides new data regarding the incidence patterns of WM in the U.S. However, further epidemiologic studies with biomarkers are needed to define the environmental, genetic, immunologic, and viral determinants of this rare but distinctive disorder. *Cancer* 1998;82:1078–81.

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Waldenström's macroglobulinemia (WM) is a malignant lymphoplasmaproliferative disorder characterized by high levels of circulating monoclonal immunoglobulin M and bone marrow infiltration by lymphoplasmacytoid cells. Although initially described more than 50 years ago,¹ little is known regarding risk factors for WM,² and descriptions of incidence patterns are sparse.³ To clarify the epidemiologic patterns of WM in the general U.S. population, we evaluated 624 cases reported to 11 population-based cancer registries over a 7-year period, and compared them with the incidence rates of other B-cell malignancies during the same time period.

METHODS

We examined the incidence of WM across 11 population-based cancer registries that participate in the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute. These registries comprise approximately 14% of the U.S. population and include the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah and the metropolitan areas of Detroit, Atlanta, Los Angeles, Seattle-Puget

TABLE 1
Incidence of Waldenström's Macroglobulinemia and Other Selected Lymphoproliferative Disorders by Race and Gender: 11 Population-Based Cancer Registries, SEER Program, 1988–1994

Diagnosis	White males		White females		Black males		Black females	
	No.	Rate ^a	No.	Rate	No.	Rate	No.	Rate
Waldenström's macroglobulinemia	326	3.6	225	1.7	16	1.7	15	1.3
Hairy cell leukemia	426	4.5	116	1.0	9	1.0	4	0.4
Multiple myeloma	4342	47.2	3941	31.2	886	107.5	875	74.4
Chronic lymphocytic leukemia	3965	43.5	2907	22.1	312	37.5	229	19.3

SEER: Surveillance, Epidemiology, and End Results Program.

^a Newly diagnosed cases per 1 million persons per year, age-adjusted using the 1970 U.S. standard.

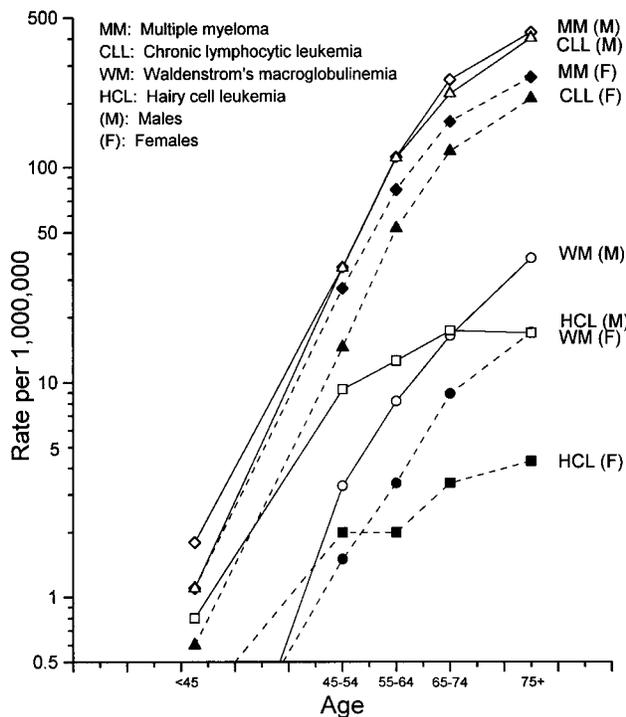


FIGURE 1. Age-specific incidence of Waldenström's macroglobulinemia and other selected lymphoproliferative disorders among whites by gender. Data from the Surveillance, Epidemiology, and End Results Program 1988–1994.

Sound, San Francisco-Oakland, and San Jose-Monterey. Patient demographic data, diagnostic information (including method of diagnosis), cancer site, and histology are among the variables routinely collected from medical records by trained SEER abstractors. Site and histology were coded according to the Second edition of the International Classification of Diseases for Oncology (ICDO-2).⁴ Cases were diagnosed from January 1, 1988, when WM (ICDO-2-9761) became report-

able, through December 31, 1994. Population estimates by age, gender, race, county, and calendar year from the Census Bureau were used to calculate incidence rates.

Age-adjusted (1970 U.S. standard) incidence rates were calculated for all ages combined and for 5 age categories (<45 years, 45–54 years, 55–64 years, 65–74 years, and 75+ years). Rates are presented in terms of new cases per 1 million persons per year, and analyzed by race, gender, age, and geographic area. Similar methods were used to calculate the incidence of other morphologically and clinically distinct B-cell malignancies reported to the SEER Program during the same time period, including multiple myeloma (ICDO-2-9732), chronic lymphocytic leukemia (ICDO-2-9823), and hairy cell leukemia (ICDO-2-9940).

RESULTS

A total of 624 cases of WM (367 males and 257 females) was diagnosed among residents of 11 SEER Program areas over the 7-year period 1988–1994, yielding incidence rates (all races combined) of 3.4 among males and 1.7 among females. A total of 560 cases (90%) were confirmed microscopically; the remaining 10% of WM diagnoses were based on clinical impressions of the treating physicians. There were 551 cases diagnosed among whites (326 males and 225 females), 31 among blacks (16 males and 15 females), 22 among other races (14 males and 8 females), and 20 with unknown race (11 males and 9 females). Thus, white males represented 52% of all cases, white females represented 36%, blacks represented 5%, other races represented 4%, and those whose race was unspecified represented 3%. The incidence rate among white males (3.6) was more than twice that reported in the other 3 major race/gender groups (Table 1). Among males, the estimated annual percent change in age-adjusted incidence was –3% (95% confidence interval [CI], –8%,

TABLE 2
Incidence of Waldenström's Macroglobulinemia among Whites in 11 Population-Based Cancer Registries: SEER Program, 1988–1994^a

Registry	Males			Females		
	No.	Rate	95% CI	No.	Rate	95% CI
Hawaii	7	7.8	(3.1–17.2)	3	2.9	(0.6–10.9)
New Mexico	25	5.3	(3.4–7.9)	13	2.1	(1.1–3.8)
Iowa	54	4.9	(3.6–6.5)	44	2.8	(2.0–3.9)
Seattle	51	4.9	(3.6–6.5)	30	2.0	(1.3–3.0)
San Jose/Monterey	19	4.0	(2.4–6.3)	12	1.7	(0.9–3.3)
Utah	14	3.2	(1.7–5.3)	7	1.0	(0.4–2.4)
San Francisco	30	3.2	(2.1–4.7)	23	1.6	(1.0–2.7)
Los Angeles	59	3.0	(2.3–3.9)	39	1.5	(1.0–2.1)
Detroit	30	3.0	(2.0–4.4)	28	1.8	(1.2–2.8)
Connecticut	29	2.5	(1.6–3.7)	21	1.1	(0.7–2.0)
Atlanta	8	2.2	(0.9–4.5)	5	1.0	(0.3–2.6)
All registries	326	3.6	(3.2–4.0)	225	1.7	(1.5–2.0)

CI: 95% confidence interval; SEER: Surveillance, Epidemiology, and End Results Program.

^aNewly diagnosed cases per 1 million persons per year, age-adjusted using the 1970 U.S. standard.

+3%). Among females, the estimated annual percent change in age-adjusted incidence was +5% (95% CI, –4%, +14%).

Incidence rates for WM increased geometrically with age among whites, with the male/female ratio being greater than one for all ages > 45 years (Fig. 1). Some geographic variation was observed among whites, with incidence rates across SEER registries ranging from 2.2–7.8 for males and 1.0–2.9 for females, but confidence limits were wide (Table 2). High rates for white males were reported in Iowa (4.9), Seattle (4.9), New Mexico (5.3), and Hawaii (7.8), although the latter estimate was based on only 7 cases. Among females, the highest rates were reported in Seattle (2.0), New Mexico (2.1), Iowa (2.8), and Hawaii (2.9), although the latter estimate was based on only 3 cases. Data for nonwhite groups were too sparse to permit assessment by age, gender, or geographic area.

As shown in Table 1, the age-adjusted incidence rates for WM were considerably lower than those reported for multiple myeloma (47.2 in males and 31.2 in females) and chronic lymphocytic leukemia (43.5 in males and 22.1 in females). The overall rates were similar to hairy cell leukemia, which was reported most often among white males (4.5). For hairy cell leukemia, the male/female and white/black rate ratios ranged between 2:1 and 4:1. All B-cell neoplasms occurred more frequently among males than females, and all except multiple myeloma were more common among whites than blacks. As shown in Figure 1, the rates for multiple myeloma, chronic lymphocytic leukemia, and WM rose sharply with advancing age in parallel with one another. Conversely, hairy cell leukem-

ia increased less steeply and tended to peak at an earlier age (range, 65–74 years), especially in men.

DISCUSSION

This survey provides new data on the incidence patterns of WM in the general U.S. population, based, to our knowledge, on the largest number ($n = 624$) of cases reported to date (89 of the cases from Seattle previously were reported by Herrinton and Weiss³). For comparison, the incidence patterns were examined for other B-cell malignancies derived from the same population and period of study. In addition to multiple myeloma and chronic lymphocytic leukemia, we included hairy cell leukemia, for which population-based incidence data⁵ are scarce. Our survey underscores the rarity of WM, particularly when compared with the more common B-cell malignancies (multiple myeloma and chronic lymphocytic leukemia), whereas the incidence of WM was similar to hairy cell leukemia. Although the rates for multiple myeloma were higher among blacks, the rates for WM were higher in whites. This contrast is interesting to note because both of these immunoproliferative tumors are believed to derive from B cells at a late stage of maturation.⁶

The time trends in the incidence of WM were unremarkable over the 7-year interval of study. This is reassuring because it would be difficult to determine whether an upward trend was real or simply due to reporting practices as a new diagnostic entity was added to SEER Program registry files. Although geographic patterns may be influenced by variations in case reporting, the distinctive features of WM make it unlikely that diagnostic factors are involved. The

dramatic increase in the incidence of WM with advancing age, which closely resembles the pattern for multiple myeloma and chronic lymphocytic leukemia, argues against serious underreporting, because a greater number of undetected cases would be expected among older patients.

The concentration of WM among white males in our survey is striking, and resembles the pattern observed in hairy cell leukemia. Although it has been suggested that hairy cell leukemia may be linked with exposures to organic solvents, petrochemicals, and related products,⁷ the role of environmental factors in WM is unclear. In one case-control study² of WM, cases were slightly better educated, but no significant differences were found for occupational exposures, alcohol or tobacco use, medication history, or prior medical conditions. An occupational lead was suggested by a clinical report⁸ of three WM cases in shoe repairers, but a large scale survey⁹ of workers exposed to benzene and other solvents in China revealed no instances of WM. The role of genetic predisposition is suggested by several reports of familial aggregation of WM,¹⁰⁻¹³ often in association with other lymphoproliferative and immunologic disorders. One study¹⁴ pointed to involvement of the interleukin-4 gene in 3 of 11 subjects tested.

The role of immunologic mechanisms is suggested by the excess risk of WM and multiple myeloma reported among patients with monoclonal gammopathy followed over time.^{15,16} Chronic antigenic stimulation² and hepatitis C virus infection¹⁷⁻¹⁹ also have been suspected to play a role in WM and other B-cell neoplasms, but the available data are limited. The possible role of viruses is underscored by a recent study linking human herpesvirus-8 with multiple myeloma and monoclonal gammopathy.²⁰ It is clear that further epidemiologic studies with biomarkers are needed to identify the environmental, genetic, viral, and immunologic determinants of this rare but distinctive disorder.

REFERENCES

1. Waldenström J. Incipient myelomatosis or "essential" hyperglobulinemia with fibrinogenopenia—a new syndrome? *Acta Med Scand* 1944;117:216–7.
2. Linet MS, Humphrey RL, Mehl ES, Brown LM, Pottern LM, Bias WB, et al. A case-control and family study of Waldenström's macroglobulinemia. *Leukemia* 1993;7:1363–9.
3. Herrinton LJ, Weiss NS. Incidence of Waldenström's macroglobulinemia. *Blood* 1993;82:3148–50.
4. Percy C, Van Holten V, Muir C. International classification of diseases for oncology. Second edition. Geneva: World Health Organization, 1990.
5. Bernstein L, Newton P, Ross RK. Epidemiology of hairy cell leukemia in Los Angeles County. *Cancer Res* 1990;50:3605–9.
6. Wagner SD, Martinelli V, Luzzatto L. Similar patterns of V-kappa gene usage but different degrees of somatic mutation in hairy cell leukemia, prolymphocytic leukemia, Waldenström's macroglobulinemia, and myeloma. *Blood* 1994;83:3647–53.
7. Staines A, Cartwright RA. Hairy cell leukaemia: descriptive epidemiology and a case-control study. *Br J Haematol* 1993;85:714–7.
8. Williamson LM, Greaves M, Waters JR, Harling CC. Waldenström's macroglobulinaemia: three cases in shoe repairers. *BMJ* 1989;298:498–9.
9. Travis LB, Li CY, Zhang ZN, Li DG, Yin SN, Chow WH, et al. Hematopoietic malignancies and related disorders among benzene-exposed workers in China. *Leuk Lymphoma* 1994;14:91–102.
10. Fraumeni JF, Wertelecki W, Blattner WA, Jensen RD, Leventhal BD. Varied manifestations of a familial lymphoproliferative disorder. *Am J Med* 1975;59:145–51.
11. Blattner WA, Garber JE, Mann DL, McKeen EA, Henson R, McGuire DB, et al. Waldenström's macroglobulinemia and autoimmune disease in a family. *Ann Intern Med* 1980;93:830–2.
12. Renier G, Ifrah N, Chevaillier A, Saint-Andre JP, Boasson M, Hurez D. Four brothers with Waldenström's macroglobulinemia. *Cancer* 1989;64:1554–9.
13. Ogmundsdottir HM, Johannesson GM, Sveinsdottir S, Einarsson S, Hegeman A, Jensson O. Familial macroglobulinemia: hyperactive B-cells but normal natural killer function. *Scand J Immunol* 1994;40:195–200.
14. Caradonna F, Barbata G, Granata G, Carbone P. Possible involvement of the IL-4 gene in Waldenström's macroglobulinemia. *Cancer Genet Cytogenet* 1994;75:153–5.
15. Axelsson U. A 20-year follow-up study of 64 subjects with M-components. *Acta Med Scand* 1986;219:519–22.
16. Kyle RA. "Benign" monoclonal gammopathy after 20–35 years of follow-up. *Mayo Clin Proc* 1993;68:26–36.
17. Santini GF, Crovatto M, Modolo ML, Martelli P, Silvia C, Mazzi G, et al. Waldenström macroglobulinemia: a role of HCV infection? *Blood* 1993;82:2932.
18. Silvestri F, Barillari G, Fanin R, Zaja F, Infanti L, Patriarca F, et al. Risk of hepatitis C virus infection, Waldenström's macroglobulinemia, and monoclonal gammopathies. *Blood* 1996;88:1125–6.
19. Zuckerman E, Zuckerman T, Levine AM, Douer D, Gutekunst K, Mizokami M, et al. Hepatitis C virus infection in patients with B-cell non-Hodgkin lymphoma. *Ann Intern Med* 1997;127:423–8.
20. Rettig MB, Ma HJ, Vescio RA, Pold M, Schiller G, Belson D, et al. Kaposi's sarcoma-associated herpesvirus infection of bone marrow dendritic cells from multiple myeloma patients. *Science* 1997;276:1851–4.