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The epidemiology of Waldenström macroglobulinemia

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ABSTRACT

Waldenström macroglobulinemia (WM) is a rare subtype of non-Hodgkin lymphoma characterized by the presence of lymphoplasmacytic lymphoma (LPL) in the bone marrow accompanied by a monoclonal immunoglobulin type M (IgM) in the serum. WM was first described only 80 years ago and became reportable in the US as a malignancy in 1988. Very little systematic research was conducted prior to 2000 to characterize incidence, clinical characteristics, risk factors or diagnostic and prognostic criteria, and there were essentially no WM-specific clinical interventional trials. Since the inaugural meeting of the International Workshop in Waldenström's Macroglobulinemia (IWWM) in 2000, WM has become the focus of a steadily increasing and productive body of research, engaging a growing number of investigators throughout the world. This introductory overview provides summary of the current understanding of the epidemiology of WM/LPL as a backdrop for a series of consensus panel recommendations arising from research presented at the 11th IWWM.

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Historical context and definition

In 1944, Jan Waldenström described 3 patients, including 2 presenting with oronasal bleeding, anemia, and lymphadenopathy, who were found to have hypofibrinogenemia, bone marrow lymphocytosis, and hyperviscosity associated with serum macroglobulinemia upon further evaluation [1]. Over the ensuing decades, Waldenström macroglobulinemia (WM) was recognized as a clinical syndrome consisting of IgM paraproteinemia associated with various types of lymphoid malignancies as well as monoclonal gammopathy of undetermined significance (MGUS). Eventually, proposals were advanced to refine the diagnosis of WM, such as defining serum IgM level thresholds to distinguish MGUS from WM [2] followed by presence of a bone marrow infiltrate and increasing monoclonal protein over time, which were found to carry more diagnostic significance [3]. Meanwhile, lymphoma classification was also evolving, and WM was associated with low-grade B-cell histologies using a variety of nomenclatures [4–8]. This evolution culminated with the World Health Organization (WHO) classification of lymphoid tumors, which categorizes WM as a subset of lymphoplasmacytic lymphoma (LPL), a rare form of non-Hodgkin lymphoma (NHL), characterized by the presence of a lymphoplasmacytic infiltrate in the bone marrow together with a monoclonal IgM in the blood [9].

Both WM and LPL may be asymptomatic or present with findings such as cytopenias, adenopathy, fatigue or B symptoms (ie, fevers, night sweats, and weight loss). WM is distinguished from LPL by the presence of IgM monoclonal gammopathy, which can manifest as hyperviscosity syndrome (including visual changes with retinopathy, skin and mucosal bleeding and variable neurological dysfunction) [10], symptomatic tissue deposition (eg, peripheral neuropathy, renal dysfunction, amyloidosis, and gastrointestinal malabsorption), or aberrant antibody activity (eg, autoimmune hemolytic anemia) [11].

To further refine diagnostic criteria for WM and to establish clinical management guidelines, a consensus panel organized in 2002 by the Second International Workshop on Waldenström's Macroglobulinemia (IWWM-2) proposed that the diagnosis of WM should be based on documentation of bone marrow involvement by LPL associated with serum monoclonal IgM and further, to classify WM patients as asymptomatic (also termed smoldering) or symptomatic [12]. The panel acknowledged the lack of pathognomonic genetic or other biomarker features and thus concluded that other entities, chiefly marginal zone lymphoma, should be considered in the differential diagnosis. Subsequently, an important advance in WM diagnostic specificity occurred in 2012 when a characteristic mutation, *MYD88* L265P, was demonstrated in up to 95+% of WM cases [13]. Further characterization of the somatic genetic landscape of WM has continued and is addressed elsewhere in this issue.

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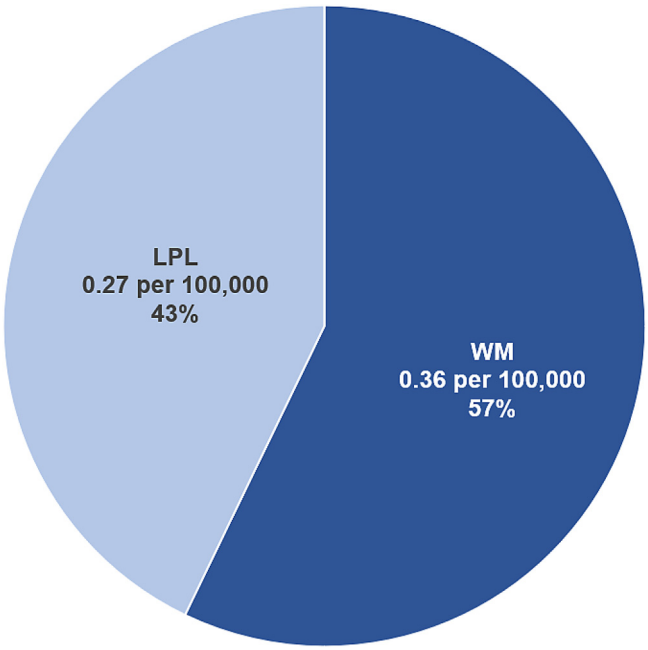

Fig. 1. Incidence Rates of Waldenström Macroglobulinemia (WM) and Lymphoplasmacytic Lymphoma (LPL) in the USA, 2000 to 2019. The incidence rates computed from SEER data correspond closely to relative frequency of cases (WM, n = 10,846; LPL, n = 8238). In contrast to the relative distribution of cases in SEER, WHO hematopathologists estimate non-WM LPL to account for only 5% of WM/LPL overall [14]. Data computed using Surveillance, Epidemiology, and End-Results Program (Surveillance Research Program, National Cancer Institute (NCI) SEER*Stat software (www.seer.cancer.gov/seerstat)), Version 8.4.0.1. Surveillance, Epidemiology, and End-Results (SEER) Program (www.seer.cancer.gov) Database: Incidence-SEER 22 Registries Research Data, Nov 2021 Submission (2000-2019). Case Selection: ICD-O-3 Histology Codes 9761 (WM) and 9671 (LPL), microscopically confirmed. Rates are per 100,000 and age-adjusted to the 2000 US Standard Population.

Incidence patterns of WM

According to the current WHO classification, WM represents the most common subtype of lymphoplasmacytic lymphoma (LPL), where the remaining LPL cases are classified as non-WM type LPL and include cases with IgG or IgA monoclonal proteins, non-secretory LPL, and IgM LPL without bone marrow involvement [14]. Together, WM/LPL accounts for approximately 2% of newly diagnosed NHL in the US, where WM became reportable as an independent malignancy in 1988 [15]. For the US, the Surveillance, Epidemiology and End Results (SEER) program collects data from selected cancer registries currently representing about 48% of the current US general population and specifically chosen to reflect its demographic composition. Using data from 2000 to 2019, the overall age-adjusted incidence of WM in the US general population is 0.36 per 100,000 (0.63 per 100,000 for WM and LPL combined (WM/LPL)). The complexity of WM as a clinicopathologically-defined entity is illustrated by differences in the proportion of WM and LPL reported by WHO pathologists [14] and observed in SEER data (Fig. 1) and likely influenced by availability of both pathology reports and laboratory data.

While rare overall, WM/LPL incidence increases markedly with age, sex and race and ethnicity (Fig. 2). WM is strongly age-dependent and is almost never diagnosed under age 30. Incidence increases beginning at age 40, and rates continue to rise with each subsequent decade. This trend is seen across all racial groups, although the rate of increase is more pronounced among Whites. The overall incidence of WM/LPL in White Americans is 0.74 per 100,000, more than double the incidence in any other racial/ethnic group. There appears to be some geographic variation in incidence. However, investigation of these observed disparities at the population level is hindered by the rarity of WM overall and differences in availability of robust cancer registry data. For non-Hodgkin lymphomas, few cancer registries provide specific morphological diagnosis for a sufficiently large proportion of cases to allow analysis by histological subtype. Rates for WM and LPL may be combined or reported separately, so comparisons must be adjusted accordingly. International comparisons based on observed data from cancer registries may also be subject to differing coding practices between registries, and definition of subtypes may be subject to regional variation [16]. Incidence rates reported for WM and LPL combined in northern Sweden from 2000 to 2012 were 50% to 75% higher (1.48 and 1.75 per 100,000, respectively, for 2 counties) compared to Sweden overall (1.05 per 100,000),[17] which is 2- to 3-fold higher than the combined rate in the US (0.61 per 100,000) for the same period. A few reports from selected Asian populations corroborate the disparities seen between Whites and Asians and Pacific Islanders in the US [18–23] (Table). However, to date there are sparse population data for other ethnicities. Finally, incidence is strongly influenced by sex. The overall incidence of WM is approximately 2-fold higher in males (0.51 per 100,000) compared to females (0.25 per 100,000) in the US. This trend persists across all racial groups, despite small numbers. The reasons for these observations are unknown and may reflect varying host or environmental factors.

The incidence of WM has increased substantially in the US over the 3 decades since WM data became reportable. The annual age-adjusted incidence increased by 65% between 1990 (0.3 per 100,000) and 2019 (0.5 per 100,000) [24]. The increase is more pronounced in males (percent change (PC) = 60.4) relative to females (PC = 47.7) and in the elderly (PC = 69.5 vs 47.7 for age 60+ and <60 years, respectively) and appears to be more prominent for Whites, although numbers for other racial groups are too small to permit comparisons. These trends are similar to those observed for NHL overall [25]. Some of this increase may be due to improved diagnostic definitions and techniques but is largely unexplained.

Etiologic risk factors

Family history

There have been few investigations of risk factors associated with WM. As discussed above, established risk factors for WM include older age, male sex, and White race/ethnicity. Family history is among the strongest and best-characterized risk factors. Familial clustering in a variety of pedigree configurations has been observed for 60 years ([26], reviewed in [27]). Within these kindred, relatives of WM patients presented with WM, related B-cell malignancies and/or IgM MGUS. WM patients in a large clinical case series reported a high prevalence (18.7%) of either WM or another B-cell disorder in first-degree relatives [28]. In a large case-control study, Vajdic and colleagues reported a 64% increased risk for developing WM/LPL in individuals with a first-degree relative diagnosed with a hematologic malignancy [29]. These observations were validated by 2 population-based registry studies that confirmed first-degree relatives of WM/LPL patients not only have a high risk for developing WM but also are at significantly increased risk to develop other B-cell malignancies [30,31]. The evidence is strongest for co-aggregation of WM with chronic lymphocytic leukemia (CLL) and other NHL, as well as MGUS. While no increased risk for Hodgkin lymphoma or multiple myeloma (MM) was seen in these studies, other Scandinavian research groups have identified increased risk of WM in relatives of patients with MM [32]. Fig. 2A and B.

Whereas there are consistent data supporting an increased risk of B-cell malignancies in relatives of WM patients, the data for

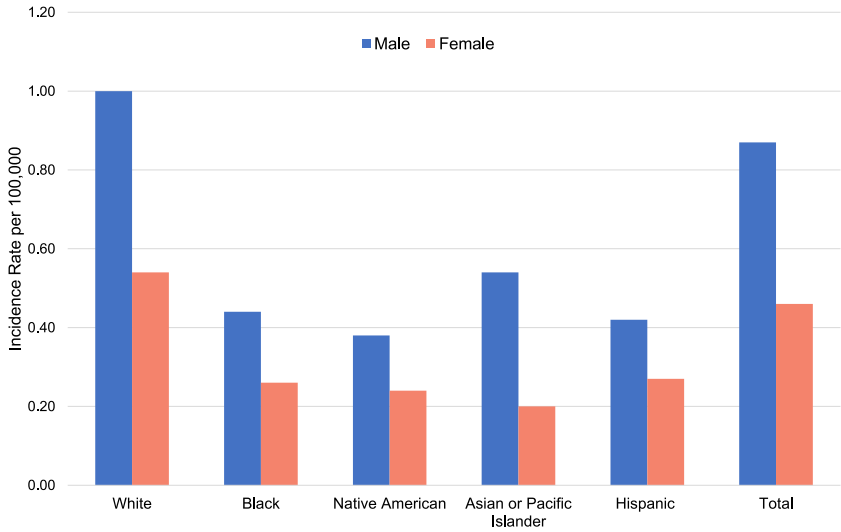

Fig. 2a. Incidence Rates of WM and LPL by Race and Ethnicity and Sex in the USA, 2000-2019 SEER Program. White, Black, Native American and Asian or Pacific Islander groups include non-Hispanic ethnicity only. Hispanic group contains all races with Hispanic ethnicity. The Native American group contains both American Indians and Alaskan Natives. Asian or Pacific Islander subgroups were too small to permit subset analysis. Data computed as described in Figure 1.

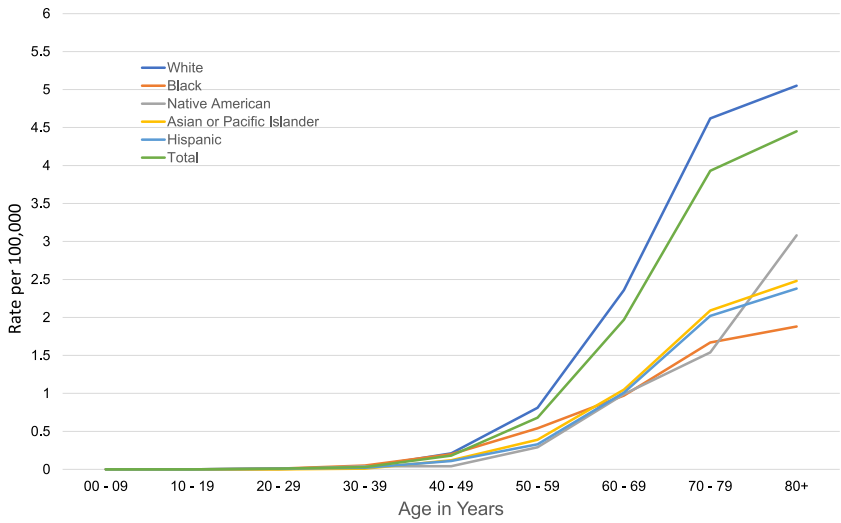

Fig. 2b. Incidence rates of WM and LPL by Race and Ethnicity and Age at Diagnosis in the USA, 2000-2019 SEER Program. White, Black, Native American and Asian or Pacific Islander groups include non-Hispanic ethnicity only. Hispanic group contains all races with Hispanic ethnicity. The Native American group contains both American Indians and Alaskan Natives. Asian or Pacific Islander subgroups were too small to permit subset analysis. Data computed as described in Figure 1.

Table
Population-based incidence rates for Waldenstrom Macroglobulinemia (WM) and Lymphoplasmacytic Lymphoma (LPL) by race and ethnicity.

	Rate per 100,000			
Country/Region	WM only	WM/LPL	Period	Reference
US Whites, 22 SEER registries	0.43	0.74	2000-2019	[20]
Olmsted County, MN, USA	0.57	–	1961-2010	[21]
South East England	0.55	–	1999-2001	[22]
Sweden – Norrbotten County	–	1.75	2000-2012	[17]
Sweden – Västerbotten County	–	1.48	2000-2012	[17]
Sweden	–	1.05	2000-2012	[17]
US Blacks, 22 SEER registries	0.16	0.33	2000-2019	[20]
US Asian or Pacific Islanders, 22 SEER Registries	0.18	0.35	2000-2019	[20]
Japan	–	0.28	2016	[19]
Japan	–	0.043	1996-2003	[18]
Taiwan	–	0.031	1996-2003	[18]
South Korea	0.03 (2003)			
	0.10 (2016)	–	2003-2016	[23]
US Hispanics, 22 SEER registries	0.17	0.33	2000-2019	[20]

Incidence for US reference populations are for non-Hispanic Whites, non-Hispanic Blacks and non-Hispanic Asian or Pacific Islanders. The Hispanic group contains all races. Numbers were too small to permit subset analysis among the Asian or Pacific Islander group. For South Korea, rates were reported per year rather than per overall period, and rates are shown for the first and last years of the study period.
Abbreviations: SEER = Surveillance, Epidemiology and End Results; US = United States

other cancers is less clear. Hanzis and colleagues noted that familial WM patients reported a significantly higher proportion of myeloid malignancy and lung cancer among their relatives as compared to WM patients without a family history, whereas sporadic WM patients were more likely than familial WM patients to report a history of prostate cancer among their relatives [33]. In contrast, in a Swedish population-based study linking family history and cancer records, no excess of myeloid malignancies (relative risk (RR) = 1.0; 95% confidence interval (CI) = 0.6–1.7) or solid tumors overall (RR = 1.08; 95% CI = 0.98–1.19) was observed among first-degree relatives of WM patients, although a borderline significantly increased risk of pancreas cancer was seen (RR = 1.8; 95% CI = 1.03–3.1; $P = .047$) [34].

IgM Monoclonal Gammopathy of Undetermined Significance (MGUS)

Monoclonal gammopathy of undetermined significance of Ig M type (IgM MGUS) is a well-established risk factor for WM (reviewed in [35]). Reliable incidence and prevalence data are modest due to imperfect ascertainment, misclassification and lack of systematic registration. The prevalence of MGUS overall varies according to age, gender, racial and geographic distribution. Using data from Olmsted County, MN [36] and a subset of the National Health and Nutritional Examination Study (NHANES) [37] the prevalence of IgM MGUS in predominantly and populations is estimated to be between 0.4% and 0.6%, which is approximately 3 orders of magnitude more common than WM. Additional data from NHANES [37], Africa [38,39] and Asia, including Japan [40], Thailand [41], Korea [42], and China [43], suggest that the racial demographic profile of IgM MGUS generally reflects that of WM.

IgM MGUS has been shown to progress to WM or a related B-cell malignancy at a rate of about 1.5% per year, with a cumulative rate of 24% at 15 years [44]. IgM MGUS is more frequent in the elderly, and therefore most patients will never progress to WM or another B-LPD. As discussed above, MGUS co-aggregates with WM, and a proportion of relatives of familial WM patients will be found to have IgM MGUS upon screening [45], but it is unknown whether progression risk is modified by family history. A few studies have addressed prognostic factors, describing M-protein size, serum albumin level, and hemoglobin level, and gender as predictors of progression [44,46-48]. However, reproducibility across studies is limited due to some differences in discriminating IgM MGUS from asymptomatic/smoldering WM. A recent study indicates the MYD88 L265P mutation can be detected in bone marrow aspirates in up to 64% of IgM MGUS patients using sensitive droplet digital polymerase chain reaction (ddPCR) methods, with a median mutational burden of 1.13% [49]. Among MYD88-positive IgM MGUS patients, 39% were also shown to carry *CXCR4* mutations (either C1013G or C1013A, at 35% and 4%, respectively). Data from these authors suggest mutation burden is correlated with progression. Additional research will help clarify the role of mutation testing in the management of IgM MGUS.

Other host and environmental factors

Accumulating evidence strongly supports a role for chronic immune stimulation in the etiology of WM. Following observations suggesting a role for hepatitis C virus (HCV) in the etiology of NHL, (reviewed in [25]) a nested case-control study in a cohort of over 700,000 US veterans demonstrated an increased risk for WM among veterans infected with HCV (adjusted hazard ratio (HR) = 2.76; 95% CI = 2.01–3.79; $P < .001$) that remained significant following Bonferroni correction [50]. Two large registry studies subsequently addressed the relationship of chronic immune stimulatory conditions and risk of WM. Koshiol and colleagues [51] conducted a nested case-control study in a cohort containing 4 million US veterans, interrogating a broad range of infectious, autoimmune and allergic conditions and adjusting for attained age, calendar year, race, and latency interval between diagnoses of the condition of interest and WM. While an early hospital-based study of 65 WM patients found no association between a personal history of autoimmune disease and subsequent risk of developing WM [52], this much larger study found that autoimmune disease was associated with a 2- to 3-fold increase in risk of subsequent WM (RR = 2.23; 95% CI = 1.68–2.97), with the excess risk appearing to be driven by autoimmune diseases that present with detectable autoantibodies. The highest observed significant risk was following a diagnosis of Sjogren syndrome (RR = 13.59; 95% CI = 4.36–42.41), followed by immune thrombocytopenic purpura (RR = 6.88; 95% CI = 2.84–16.64), Crohn disease (RR = 6.68; 95% CI = 2.76–16.20), rheumatoid arthritis (RR = 2.09; 95% CI = 1.22–3.57), and chronic rheumatic heart disease (RR =1.94; 95% CI = 1.12–3.39). A history of any infection was not associated with increased risk, with a few significant exceptions including human immunodeficiency virus (HIV), (RR = 12.05; 95% CI = 2.83–51.46), hepatitis (RR = 3.39; 95% CI = 1.38–8.30), and rickettsiosis (RR = 3.35; 95% CI = 1.38–8.14). No association was seen for allergic conditions.

Kristinsson et al [53] analyzed data from 2470 WM/LPL patients, 9698 matched controls and nearly 30,000 first-degree relatives of cases or controls within the Swedish linked population-based registries and confirmed an association with Sjögren syndrome (odds ratio (OR) = 12.1; 95% CI = 3.3–45.0) while extending observations to include associations with other autoimmune diseases including systemic sclerosis (OR = 4.7; 95% CI = 1.4–15.3), autoimmune hemolytic anemia (OR = 24.2; 95% CI = 5.4–108.2), polymyalgia rheumatica (OR = 2.9; 95% CI = 1.6–5.2), and giant cell arteritis (OR = 8.3; 95% CI = 2.1–33.1). A personal history of various infectious diseases, including pneumonia (OR = 1.4; 95% CI = 1.1–1.7), septicemia (OR = 2.4; 95% CI = 1.2–4.3), pyelonephritis (OR-1.7; 95% CI = 1.1 = 2.4) sinusitis (OR = 2.7; 95% CI = 1.4–4.9; herpes zoster (OR = 3.4; 95% CI = 2.0–4.5) and influenza (OR-2.9; 95% CI = 1.7–5.0), was associated with increased risk for WM/LPL. In addition, a family history of certain autoimmune or infectious diseases conferred increased risk of WM/LPL.

A large international consortium found various other factors associated with increased risk of developing WM/LPL in multivariate analysis, including personal medical history of certain autoimmune disorders including Sjögren syndrome (OR = 14.0; 95% CI = 3.60–54.6; $P = .002$) and systemic lupus erythematosus (OR = 8.23; 95% CI = 2.69–25.2; $P = .003$) in addition to occupation as a medical doctor (OR-5.54; 95% CI = 2.19–14.0; $P = .002$) or forestry worker, based on small numbers [29]. In this study 2 exposures, hay fever and highest quartile of usual adult weight (OR = 0.73 and 0.61, respectively) were inversely associated with risk for WM/LPL. Risk increased in nonsignificant trend fashion with duration of cigarette smoking, and no association was seen with risk of WM/LPL with any other type of farming or animal-related occupation or residence, hair dye use in women, sun exposure or any measure of alcohol use.

Finally, evidence suggests that familial WM may be modulated in some instances by additional exposures aside from family history. Royer et al [54] conducted a family-based analysis using unaffected relatives as controls. In their data, familial WM patients were significantly more likely than their unaffected relatives to report a personal history of autoimmune disease (OR = 2.27; 95% CI = 1.21–4.28), any of certain specified infections OR = 2.13; 95% CI = 1.25–3.64), or any allergy (OR = 1.94; 95% CI = 1.09–3.46), as well as history of exposure to farming (OR 2.70; 95% CI = 1.34–5.43), pesticides (OR = 2.83; 95% CI = 1.56–5.11), organic solvents

(OR = 4.21; 95% CI = 1.69–10.51) or wood dust (OR = 2.86; 95% CI = 1.54–5.33). No association was seen with ever smoking, ever alcohol use or hair dye.

Genetic epidemiology

In part due to its rarity and the difficulty in assembling large case sets, the genetic basis for predisposition to WM was first investigated in the familial setting. These efforts have proved challenging for several reasons. First, large informative WM families are rare, with the most commonly observed pedigree configuration consisting of 2 affected individuals. As additional families have been accrued at the National Cancer Institute and elsewhere, larger and more complex pedigree configurations have been observed. Multi-generational pedigrees support a role for genetic factors in WM predisposition, and the diversity of reported inheritance patterns (eg, parent-offspring, siblings-only, avuncular, and cousins), sometimes with apparently skipped generations, suggests variable penetrance and/or genetic heterogeneity. Evaluation of inheritance patterns and segregation is complicated by the late age at onset of the disease in addition to the fact that WM was first recognized, and modern diagnostic criteria developed, only comparatively recently. Confirmation of WM familial clustering and co-aggregation of related B-cell disorders in large populations suggests susceptibility gene(s) may be operating at an early stage of B-cell development with possible pleiotropic effects.

Chromosomal abnormalities occur in WM patients, who present with a median of 2 to 3 events [55]. The most frequent abnormality is deletion of 6q (del6q), which occurs in 30% to 50% of WM patients and is associated with increased risk of progression to symptomatic disease [56]. Various other chromosomal aberrations occur at much lower frequencies, including trisomy 4, trisomy 8, trisomy 12, and deletions of 13q and 17p [55,57-65]. Balanced translocations are not a feature of WM in contrast to many other B-cell lymphoproliferative disorders (B-LPD). These cytogenetic abnormalities have been described as features of the tumor clone. In contrast, early cytogenetic studies of germline events in family clusters were inconclusive [66–68]. In 1 family-based study, investigators examined bone marrow and peripheral blood from familial WM and IgM MGUS patients and found a small number of recurrent deletion events [69]. Only one of these was found in both tumor and peripheral blood mononuclear cells, and none were seen in IgM MGUS patients or shared among WM patients within the same kindred. Another study documented a high frequency of del6q21 by FISH in tumor cells from both familial and nonfamilial patients but did not assess the germline [28].

The first genome-wide effort to identify regions containing susceptibility genes was a linkage analysis conducted in 11 informative, well-characterized WM families using a dense array of microsatellite markers [70]. Parallel analyses of WM alone and WM together with IgM MGUS as an expanded phenotype found evidence for linkage to 4 chromosomal regions, including 1q, 3p, 4q and 6q, with stronger evidence for linkage when IgM MGUS was included in the model. In a complementary candidate gene association analysis, single nucleotide polymorphisms (SNPs) in 5 genes (BCL6, IL10, IL6, IL8Ra and TNFSF10) were significantly and robustly associated with WM [71]. Together, these studies suggest genetic heterogeneity underlying WM.

Germline variation in a few other genes including specific human leucocyte antigen (HLA) haplotypes [66,72] and hyaluron synthase 1 (*HAS1*) splicing variants [73,74] have been implicated as potentially contributing to WM risk in a few small studies. Additional research is needed for confirmation.

An interesting line of research has focused on the targets of paraproteins as risk factors for development of IgM MGUS and WM. Paraproteins from approximately 10% of patients with either IgM MGUS or WM were shown to react specifically with hyperphosphorylated paratarg-y (pP-7) [75]. Paratarg proteins may be constitutively hyperphosphorylated in an autosomal dominant fashion. Resultant chronic antigenic stimulation from exposure to this abnormal autoantigen is hypothesized to account for familial clustering. In a follow-up study in Sweden [76], pP-7 carrier state was documented in 19% of familial WM cases, with 9.5% having pP-7-reactive antibodies. In contrast, 7.1% of nonfamilial WM cases and 42.9% of healthy relatives in 2 WM families were shown to carry pP-7, with reactivity shown in 7.1% and 0%, respectively. These intriguing findings deserve further study in larger longitudinal cohorts.

With the advent of massively parallel sequencing technology, whole-exome and whole-genome sequencing (WES and WGS, respectively) of informative families was performed to identify rare, high-penetrance germline mutations that might contribute to WM predisposition. A major advance occurred with the identification by WGS of a characteristic mutation, $MYD88^{L265P}$, which was found to be a key somatic event in WM tumorigenesis [13]. Subsequent targeted sequencing in familial WM patients failed to detect this mutation in the germline, confirming that it is not an inherited susceptibility gene [77]. Despite the promise of these methodologies, to date results have been disappointing. Potentially deleterious rare variants in 2 genes, *LAPTM5* and *HCLS1*, co-segregating with disease and enriched in familial versus nonfamilial WM cases have been described in a single family [78]. A recent analysis of a pair of identical twins, one presenting with WM and the other with IgM MGUS, identified *FHL2* as another candidate susceptibility gene [79]. While promising, as yet these variants have not been reported in additional families. Thus, it remains to be seen whether highly penetrant rare variants in any gene(s) will be found to recur across multiple families or remain private to individual kindred.

The accumulating evidence for genetic heterogeneity suggests a role for common genetic variation in WM etiology. A genome-wide association study (GWAS) performed recently leveraged familial cases to enrich an otherwise small sample for susceptibility loci [80]. Two loci were identified, at chromosomes 6p25.3 and 14q32.13, respectively, and replicated in a nonfamilial sample. These loci were notable for the magnitude of their effect size; in the meta-analysis, the 6p25.3 locus conferred a 20-fold increase in risk (OR 21.1; 95% CI = 14.4–31.0; $P = 1.36 \times 10^{-54}$) and the 14q32.13 locus was associated with a 5-fold excess risk (OR 4.9; 95% CI = 3.5–7.0). Functional evaluation produced evidence suggesting a potential mechanism for the 6p25.3 locus, possibly through short-range effects on *EXOC2* or long-range interaction with the *IRF4* promoter. Interestingly, the lead SNP on 6p is the same as the top SNP reported for diffuse large B-cell lymphoma (DLBCL) [81]. Validation studies in a larger sample set are currently in progress.

Outcomes

Second malignancies and WM

Various secondary malignancies have been observed following a diagnosis of WM, suggesting possible influence of shared genetic or environmental factors and/or treatment effects. Among 230 patients In an Italian case series, 10% developed a new solid tumor primary, including lung, gastrointestinal, urinary tract, prostate, breast, brain, and thyroid [82]. Another 4% developed a second hematologic malignancy, including DLBCL (n = 6), myelodysplastic syndrome/acute myeloid leukemia (MDS/AML, n = 3), and chronic myeloid leukemia (CML, n = 1). Five of 6 patients developing DLBCL and all patients with MDS/AML had been previously treated with either alkylating agents or alkylators and nucleoside analogs.

Standardized incidence ratios (SIRs) were significantly elevated for all cancers (SIR = 1.69; 95% CI = 1.19–2.38), brain (SIR 8.05; 95% CI = 2.01–32.19), DLBCL (SIR = 9.24; 95% CI = 4.1–20.5), and MDS/AML (SIR = 8.4; 95% CI = 2.7–26), but the estimates were imprecise for specific sites due to small numbers. Subsequent analysis of 4676 WM/LPL patients using SEER data from 1992 through 2011 confirmed significant excess risk of second solid cancers overall (SIR = 1.20; 95% CI = 1.10–1.32), as well as site-specific excess of second thyroid (SIR = 2.67; 95% CI = 1.28–4.92), lung (SIR = 1.48; 95% CI = 1.21–1.80), and urinary tract (SIR = 1.41; 95% CI = 1.08–1.81) cancers [83]. Significant risk was also seen for melanoma (SIR = 1.94; 95% CI = 1.35–2.69). Risk was increased more than 4-fold for all hematologic cancers, with 3- to 4-fold excess risk observed for all tested subcategories, including aggressive NHL, indolent NHL, MM, and acute leukemia. SEER does not have complete ascertainment of treatment data, so the effect of prior therapy could not be assessed, although there was no difference in overall risk for patients diagnosed before or after 2000.

Survival

Symptomatic WM/LPL patients are candidates for treatment [84]. Treatment approaches, which have evolved to include (alone or in combination) alkylating agents and nucleoside analogs, monoclonal antibodies, proteasome inhibition and newer targeted therapies (eg, Bruton Tyrosine Kinase inhibitors (BTKi), B-cell lymphoma-2 (BCL2) inhibitors) [85], have improved survival [86,87].

Several studies suggest family history impacts prognosis and outcomes. Family history is an independent predictor of disease progression and is associated with a 1.3-fold increased risk of death compared to sporadic WM, with an increasing hazard ratio for each additional relative with a B-LPD (WM, CLL, MM, NHL or MGUS) [88]. Familial patients have been noted to have greater bone marrow involvement and baseline IgM level but not significant differences in cytogenetic abnormalities or presenting symptoms or signs [28,54,69]. A single institution study found family history of WM was correlated with response rates and time to next therapy and/or progression following rituximab- versus bortezomib-containing regimens but did not address survival [89].

A growing body of evidence supports the predictive impact of various genetic events, including *MYD88* and *CXCR4* mutation status (reviewed in [90]) and cytogenetic abnormalities (specifically del6q) [91], on prognosis, including treatment response indicators, risk of histological transformation [92], and survival.

A limited number of studies have addressed cause-specific survival, recognizing that the late onset characteristic of WM may lead to confounding of survival analyses by competing risks for mortality. Initial case series attributed significant mortality to conditions other than WM/LPL such as second malignancies and infections but had limited detail regarding cancers other than lymphoma and non-cancer conditions [93,94]. Following a registry-based study that attributed the majority of deaths in WM patients to lymphoma, solid tumors and cardiac conditions [95], a comprehensive analysis of cause-specific survival was performed [96]. In this study, lymphoma deaths predominated among patients younger than 65 years (23.2%; 95% CI = 20.3%–26.0%) at 16 years following WM/LPL diagnosis, whereas the cumulative mortality for non-cancer deaths increased with age, reaching 48.7% (95% CI = 45.8%–51.7%) for patients aged ≥75 years. Patients with WM/LPL had a 20% higher risk of death due to non-cancer causes compared to the general population (standardized mortality ratio 1.2; 95% CI = 1.1–1.2; excess absolute risk 46.8) that was driven by significant excess risks for infections, respiratory and gastrointestinal diseases.

Conclusions

During the 80 years following the first description of WM, substantial progress has been made in understanding the epidemiology and etiology of WM, as well as advances in methods for diagnosis, prognostic assessment and therapy. The incidence, distribution and survival patterns of WM/LPL show distinctive variation by age, sex, and race/ethnicity. These patterns, though still poorly understood, strongly suggest that genetic, infectious, environmental, and possibly lifestyle factors in addition to other host factors are important in the etiology of WM/LPL. Intensive research efforts have led to a better understanding of both etiologic heterogeneity and the common threads of chronic antigenic stimulation and immune dysfunction that underpin WM/LPL susceptibility. Despite undeniable progress, however, critical questions remain and warrant further investigation. Continued epidemiologic research is imperative to evaluate these factors and should include widespread collaborative and consortial efforts with incorporation of tissue collection and new technologies to investigate specific etiologic factors.

Conflict of interest

The author has no conflicts of interests to disclose.

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