bjh review

Chronic lymphocytic leukaemia: an overview of aetiology in light of recent developments in classification and pathogenesis

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Summary

This overview of the epidemiology of chronic lymphocytic leukaemia (CLL) summarizes the evolution of classification and coding systems and describes the intersection of pathogenesis and aetiology. The role of the putative precursor to CLL, monoclonal B-cell lymphocytosis (MBL), is considered, and ideas for future investigations of the MBL-CLL relationship are outlined. We discuss the epidemiology of CLL, focusing on descriptive patterns and methodological considerations. Postulated risk factors are reviewed including the role of ionizing and non-ionizing radiation, occupational and environmental chemical exposures, medical conditions and treatments, and lifestyle and genetic factors. We conclude by raising key questions that need to be addressed to advance our understanding of CLL aetiology. Recommendations for future epidemiological studies are given, including the standardization of reporting of CLL across cancer registries, the clarification of the natural history of MBL, and the circumvention of the methodological shortcomings of prior epidemiological investigations in relation to radiation, chemical exposures and infectious agents.

Keywords: chronic lymphocytic leukaemia, aetiology, radiation, chemicals, review.

Mature B-cell neoplasms are clonal proliferations of B-cells at various stages of differentiation, ranging from naïve B-cells to mature plasma cells (Jaffe *et al*, 2001). B-cell chronic lymphocytic leukaemia (hereafter designated CLL) accounts for approximately 30% of mature B-cell malignancies (SEER-9, 2007). Despite the designation of CLL as a single entity, it is characterized by biological, clinical and cytogenetic heterogeneity.

Recent scientific advances have provided new understanding of key aspects of the development, maturation and evolution of normal B-cell subpopulations, and the likely origin of CLL within the B-cell differentiation scheme (Chiorazzi *et al*, 2005; Klein & Dalla-Favera, 2005; Staudt & Dave, 2005). These and similar breakthroughs for other haematopoietic malignancies and related conditions led to a major revision of the classification scheme for all lymphoid and myeloid disorders. The resulting World Health Organization (WHO) classification incorporates cell lineage, morphology, immunophenotype, genetics and clinical features (Jaffe *et al*, 2001). In light of these major scientific developments, it seems timely to reconsider key aspects of the epidemiology of CLL together with its similar counterpart, small lymphocytic lymphoma (SLL), which are considered different manifestations of the same lymphoid neoplasm in the WHO classification (Jaffe *et al*, 2001).

This overview of the epidemiology of CLL includes three sections. The first section describes the evolution of classification and coding systems, the intersection of pathogenesis and aetiology, and the putative precursor of CLL, monoclonal B-cell lymphocytosis (MBL). The second section briefly characterizes the epidemiology of CLL, including descriptive patterns; the role of animal models in identifying risk factors, genetic pathways and biological mechanisms; and discusses known risk factors based on our current, albeit limited, understanding of aetiology. Descriptive and analytical epidemiological research on CLL is also considered in more detail in the accompanying reports by Dores *et al* (2007), Schubauer-Berigan *et al* (2007), Blair *et al* (2007) and Landgren *et al* (2007a). The third section poses key questions pertinent to CLL aetiology and provides recommendations for future epidemiological studies.

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Classification, pathogenesis and putative precursor

Classification and coding

Chronic lymphocytic leukaemia has been recognized as a distinct clinical entity for almost 100 years (Osler, 1909). However, disease classification systems did not systematically begin to distinguish 'chronic' from 'acute' forms of leukaemia until the late 1960s, with the adoption of the International Classification of Diseases (ICD), Eighth Revision (ICD 1967). The absence of standardized disease definitions, staging schemes, and markers of disease behaviour hampered clinical trials and epidemiological studies of CLL until the mid-1970s. Proposals for staging systems in the 1970s (Rai *et al*, 1975; Binet *et al*, 1977) followed by clinical trial guidelines in the 1980s and 1990s (Binet *et al*, 1981; Cheson *et al*, 1988, 1996; International Workshop on CLL 1989) facilitated advances in treatment and understanding of CLL biology. Clinical and epidemiological investigations also benefited from implementation of the French-American-British classification of chronic B- and T-cell leukaemias, which incorporated information on morphology and cellular membrane phenotype (Bennett *et al*, 1989), and from the Kiel classification, which utilized grade and grouped CLL with low-grade B-cell lymphomas (Lennert *et al*, 1975). Improved knowledge of normal B- and T-cell differentiation and genetic changes led to the Revised European and American Lymphoma classification in the mid-1990s (Harris *et al*, 1994), followed by the WHO classification of all haematopoietic and lymphoproliferative disorders (HLD) (Jaffe *et al*, 2001).

Epidemiological studies of CLL and other HLD have been influenced by evolving classifications as they are translated to internationally recognized coding schemes. The long-standing ICD, with its subsequent revisions, continues to be used to code discharge diagnoses (except cancers) of hospitalized patients and death certificates. The ICD is of limited use for epidemiological studies of CLL and other HLD because information on key biological and clinical characteristics (including immunophenotype, cytogenetics and molecular characteristics) is not incorporated. In contrast, the ICD for Oncology (ICD-O), which was first introduced in the mid-1970s and subsequently revised in 1990 and 2000, has increasingly converged with HLD classifications developed by expert haematopathologists through the incorporation of information on cell lineage, immunophenotype, cytogenetics and clinical features. The current ICD-O-3 (Fritz *et al*, 2000) mirrors the WHO classification (Jaffe *et al*, 2001) to a high degree, although ICD-O-3 continues to consider CLL and SLL separately as did the earlier versions, ICD-O (WHO 1976) and ICD-O-2 (Percy *et al*, 1990).

The WHO classification (Jaffe *et al*, 2001) groups CLL with SLL based on their identical cytology, tissue histopathology, immunophenotype and cytogenetics. CLL/SLL consists of monomorphic small, round B lymphocytes in the peripheral blood, bone marrow and lymph nodes, with admixed prolymphocytes and paraimmunoblasts organized in characteristic pseudofollicular proliferation centres (pseudofollicles) in tissue sections. Diagnostic criteria for CLL include involvement of the bone marrow with a clonal B-cell population and presence in the peripheral blood of an absolute lymphocytosis, with lymphocyte counts of $>5 \times 10^9$/l (Cheson *et al*, 1988, 1996) or $>10 \times 10^9$/l (International Workshop on CLL 1989; Jaffe *et al*, 2001). The diagnosis of SLL is restricted to cases with the characteristic features of CLL, including tissue morphology and immunophenotype, but with absence of involvement of the peripheral blood.

The characteristic immunophenotype of lymphoid cells in CLL/SLL is weak surface IgM, with or without IgD, positive for surface CD5, CD19, CD20 (weak), CD22 (weak), CD79a, CD23, CD43 and CD11c (weak), and negative for CD10 and cyclin D1. As mantle cell lymphoma can be accompanied by leukaemic involvement of the peripheral blood and has a similar immunophenotype, a lymph node biopsy and cytogenetic studies are sometimes necessary to exclude this diagnosis.

Intersection of pathogenesis and aetiology

Although traditionally thought to be derived from naïve B-cells, recent studies (Chiorazzi & Ferrarini, 2003; Stevenson & Caligaris-Cappio, 2004; Chiorazzi *et al*, 2005; Klein & Dalla-Favera, 2005) support the derivation of CLL from activated, antigen-experienced B-cells (Table I). Auto-antigens or super-antigens derived from pathogenic microorganisms have long been thought to play a role in the pathogenesis of this disease (Conley *et al*, 1980; Linet *et al*, 1986; Rosenblatt *et al*, 1991; Doody *et al*, 1992; Messmer *et al*, 2004; Thorselius *et al*, 2006; Stamatopoulos *et al*, 2007). However, a recent population-

Table I. Evidence for antigen stimulation in chronic lymphocytic leukaemia (CLL).

Cell surface phenotype resembles antigen-experienced and activated B-cells (increased CD23, CD25, CD69, CD71 and CD27; decreased CD22 FcγR11b, CD79b and IgD)
Expression of CD38 and ZAP-70 is associated with increased B-cell receptor complex signalling
Biased or preferential use of certain *IGHV* genes (*IGHV1-69*, *IGHV3-07*, *IGHV3-23*, *IGHV4-34* and *IGHV4-39*) during VDJ recombination
Biased use of *IGHV* genes in unmutated (*IGHV1-69* and *IGHV4-39*) and mutated subtypes (*IGHV3-07*, *IGHV3-23* and *IGHV4-34*) with evidence of progressive mutations
Presence of stereotyped antigen receptors in a subset of patients
Production of polyreactive and autoreactive antibodies cells against common antigens by CLL

based epidemiological study found little evidence linking autoantigens with development of CLL (Landgren *et al*, 2006). The initiating genetic lesion of CLL probably occurs in an immature bone marrow B-cell. Subsequent repetitive antigenic stimulation probably leads to additional genetic lesions that result in neoplastic transformation to leukaemia (Chiorazzi *et al*, 2005). Alternatively, the initiating lesion in CLL could occur in immature B-cells circulating in the peripheral blood, or in similar B-cells that have homed to lymph nodes or the spleen in SLL.

The nature of B-cell receptor signalling appears to be linked with clinical outcome because patients with unmutated *IGHV* genes have significantly shorter survival than those with mutated genes (Damle *et al*, 1999; Hamblin *et al*, 1999; Degan *et al*, 2004). ZAP-70, a signalling molecule on normal T-cells and natural killer (NK) cells but not B-cells, is expressed anomalously in CLL with unmutated *IGVH* genes and may enhance the signalling process when the B-cell receptor is engaged (Hamblin, 2004). Gene expression profiles and clinical studies have shown that ZAP-70 expression is highly correlated with the unmutated subtype of CLL and is also an adverse predictor of survival (Klein *et al*, 2001; Rosenwald *et al*, 2001). Some investigators have suggested that a subset of mutated CLL is derived from memory B-cells that have transited through germinal centres (Klein *et al*, 2001). However, recent data support the idea of CLL originating from B-cells of the early primary immune response and/or T-cell independent immune response (Chiorazzi *et al*, 2005; Herve *et al*, 2005). Despite variation in survival among patients with different mutational subtypes, all forms of CLL appear to share a common gene expression signature that suggests a common cell of origin and/or mechanism of transformation regardless of mutational status (Klein *et al*, 2001; Rosenwald *et al*, 2001).

Putative CLL precursor: MBL

Using flow cytometry, investigators have identified very small, circulating B-cell clones with a surface phenotype similar to CLL in some healthy persons (Han *et al*, 1984; Montserrat *et al*, 1988; French Cooperative Group on Chronic Lymphocytic Leukaemia 1990; Marti *et al*, 1992, 2005; Vogt *et al*, 1995; Rawstron *et al*, 2002a; Shim *et al*, 2007). With the exception of an increasing occurrence of MBL with advancing age (Rawstron, 2004) and in first-degree relatives of patients with CLL (Rawstron *et al*, 2002a,b; Marti *et al*, 2003; de Tute *et al*, 2006), population subgroups at risk for developing MBL have not been identified. Although many terms have been used to describe this condition, it has been recently designated 'MBL'. A proposed working definition of MBL is the presence of a monoclonal B-cell population detected by flow cytometry in persons not meeting the diagnostic criteria for other B-lymphoproliferative disorders (Marti *et al*, 2005).

The risk factors for MBL are unknown, and its natural history has not been systematically examined. With increasing recognition of MBL but absence of detailed information on the descriptive epidemiological patterns and progression of this potential precursor, it is timely to consider a conceptual framework that may clarify our understanding of the origin, natural history and interrelationships of MBL with CLL and other conditions (Fig 1). In this model, the onset of MBL may be followed by four possible outcomes: progression to CLL, other HLD or other medical condition; persistence of MBL without progression; gradual resolution of MBL in concert with other manifestations of immune senescence; or regression of MBL with no apparent evidence of an associated decline in immune response.

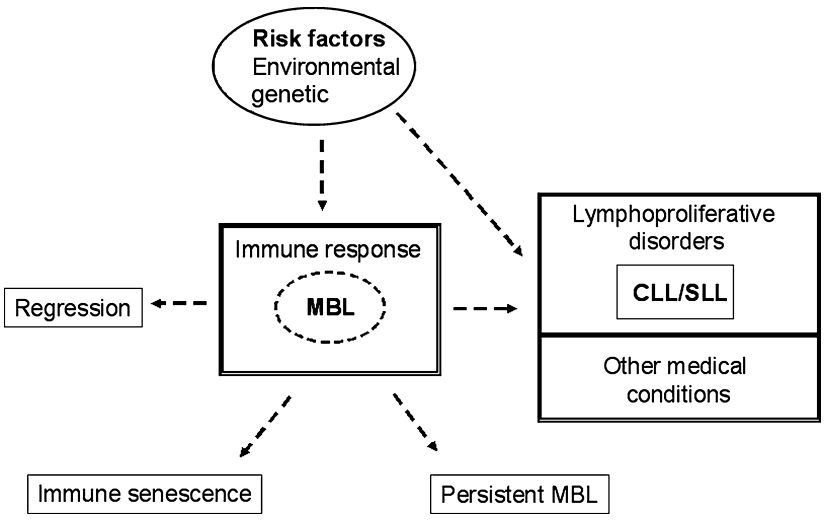

Fig 1. Relationship of monoclonal B-cell lymphocytosis (MBL) and chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL).

Epidemiology of CLL: descriptive patterns, animal models and risk factors

Descriptive patterns

Dores *et al* (2007) have conducted the first large-scale effort to evaluate CLL and SLL separately and combined. Among more than 20 000 CLL and SLL cases diagnosed during 1987–2004 in the National Cancer Institute's (NCI) Surveillance Epidemiology and End Results (SEER) population-based registries in the United States, incidence rates for both lymphoproliferative disorders increased exponentially with age, and rates were substantially higher for CLL than for SLL among all gender-race groups studied. Age-adjusted incidence rates for CLL and SLL were 70–90% higher among males than females, but 25–28% and 69–80% lower among African-Americans and Asian/Pacific Islanders respectively, compared with caucasians. These race-specific differences in incidence rates in the US are consistent with the characteristics described in the corresponding native populations in the countries of origin (Finch & Linet, 1992; Sgambati *et al*, 2001; Linet *et al*, 2006). Low incidence rates persist among individuals migrating to the US from Asian countries and their descendants (Herrinton *et al*, 1996; Gale *et al*, 2000; Pan *et al*, 2002).

Dores *et al* (2007) were also the first to confirm evidence of delayed reporting of CLL, but not SLL, to the SEER registries. The delay was attributed to the increasing proportion of CLL patients diagnosed in outpatient settings and the growing use of automated blood count and flow cytometry instruments to establish the diagnosis. After correcting for delayed reporting, these investigators found no evidence that CLL incidence was declining as was reported in earlier studies (Groves *et al*, 1995; Linet *et al*, 2006; Morton *et al*, 2006). Because there was only a modest increase over time in the proportion of CLL cases diagnosed by flow cytometry and reported to the SEER registries, these investigators postulated that SEER incidence rates probably reflected under-reporting and incomplete case ascertainment. Dores *et al* (2007) concluded that changing medical care patterns have probably complicated accurate estimation of CLL incidence and comparison of US rates and trends with those in other populations internationally. The findings and conclusions from evaluation of SEER registry data are supported by the report of a 38% higher incidence of CLL in the Central Arkansas Veterans Healthcare System database than that reported to the central tumour registry (Zent *et al*, 2001). Similarly, a comparison of the level of ascertainment of lymphoproliferative malignancies in hospitals *versus* a large population-based cancer registry during 1964–2003 in Sweden found approximately 12% under-ascertainment of CLL in the cancer registry compared with the hospitals. Under-ascertainment was particularly pronounced among patients diagnosed at older ages and with early stage disease (Turesson *et al*, 2007). It is notable that even in a country with universal health care, the under-ascertainment rate of CLL (e.g. reporting from the hospitals to the central Swedish Cancer Registry) did not change over the study period, which is further reflected by stable CLL incidence rates over the past decades (http://www.socialstyrelsen.se).

Animal models

Animal studies can provide initial clues about potential leukemogens, strengthen evidence when human studies are limited, and yield comparative results in different populations of the same animal or across species to assess reproducibility and inter-species extrapolation. Studies in animals can clarify exposure-disease relationships for rare outcomes, such as CLL, and for inconsistent results among epidemiological studies. Blair *et al* (2007) summarize the literature on 100 chemicals that have been reported to cause HLD in at least one sex in one animal species (Gold *et al*, 2001). Further information on the potential leukemogenicity of chemicals and other agents tested can be found on the National Toxicology Program website (http://ntp.niehs.nih.gov/index.cfm; accessed on July 21, 2007). In addition, information on more than 900 agents evaluated for potential carcinogenicity by the International Agency for Research on Cancer is detailed in a comprehensive monograph series (http://monographs.iarc.fr/ENG/Monographs/allmonos90.php; accessed on July 21, 2007). Because specific HLD display different descriptive epidemiological patterns and risk factor profiles, care should be taken in interpreting toxicological and carcinogenicity study findings across animal models with different lymphoproliferative or myeloid malignancies.

Animal models can also be helpful for elucidating pathogenesis, clarifying genetic mechanisms, and identifying individual and joint effects of genetic and exogenous agents that initiate or promote CLL. Certain genetic strains may arise *de novo*, such as the New Zealand Black (NZB) mouse model, which is characterized by B-cell hyperproliferation and autoimmunity early in life and subsequent progression to late-onset CLL (Phillips *et al*, 1992). Animal models can also be genetically engineered, such as the transgenic mouse models of CLL that have been developed in the past few years (Scaglione *et al*, 2007). Such transgenic models may provide further insight into the molecular mechanisms underlying the pathogenesis of CLL (Pekarsky *et al*, 2007). Mouse models provide evidence for the deregulation of three important genetic pathways, i.e. the Tcl1-Akt pathway, the tumour necrosis factor–nuclear factor (NF)-κB pathway, and the Bcl2-mediated anti-apoptotic pathway in CLL. Raveche *et al* (2007) have also recently reported that altered expression of microRNAs mir-15a/16-1 (the region of genetic synteny with the mouse D14mit160 chromosomal region is the chromosome 13q14 region) in humans appears to be the molecular lesion in CLL. Toxicological studies of chemicals and other agents implicated as possible risk factors for CLL have not been carried out in NZB mice.

Known and putative risk factors

Ionizing and non-ionizing radiation. Ionizing radiation has been linked with increased risk of leukaemia for almost 100 years. Early key radiation epidemiological studies, which mostly focused on mortality outcomes, often reported notable excess risks of leukaemia without specifying cell type. Other early studies that evaluated leukaemia mortality by subtype found excesses of acute leukaemias and chronic myeloid leukaemia, but not CLL (Court-Brown & Doll, 1965; Finch *et al*, 1969; Ischimaru *et al*, 1969). In more recent epidemiological studies of radiation-exposed populations, the higher proportion of death certificates with leukaemia subtype designation and studies evaluating cancer incidence outcomes have led to more frequent reporting of radiation-related risks and dose-response for leukaemia subtypes, including CLL. To date, there has been no separate assessment of SLL from larger grouped categories of non-Hodgkin lymphoma (NHL) in relation to ionizing radiation.

Most, but not all, studies of populations exposed to medical, occupational or environmental sources of ionizing radiation have not found evidence linking CLL with radiation exposure, although inadequate statistical power, limited duration of follow-up, and other methodological issues (see below) frequently preclude findings of a statistical association (Richardson *et al*, 2005; Silver *et al*, 2007). A few studies of medical radiotherapy, including those of patients with ankylosing spondylitis (Weiss *et al*, 1995; Wick *et al*, 1999) and women treated for uterine bleeding (Inskip *et al*, 1990, 1993), have reported elevated risks of CLL or unspecified lymphatic leukaemia, although not all of these studies demonstrate dose-response relationships and some are limited by small numbers and incomplete specification of leukaemia subtype for the subgroup of patients with lymphatic leukaemia. A cohort mortality study of radiation workers employed in nuclear technology development showed a significant dose-response relationship for CLL (Boice *et al*, 2006); however, CLL mortality was not linked with occupational radiation exposure in other large cohorts of nuclear workers (Cardis *et al*, 1995, 2007), although these large, multi-country studies included only a few cases of CLL with exposure to substantial estimated radiation doses (e.g. ≥100 mSv). Recently, a case-control study of leukaemia incidence among uranium miners found a positive association of CLL with cumulative radon exposure (Rericha *et al*, 2006), and an ecologic study of radon exposure in Iowa, a SEER catchment area, demonstrated a weak association with CLL (Smith *et al*, 2007a).

The excess risks of acute leukaemias and chronic myeloid leukaemia within a few years of radiation exposure, but no comparable increase in risk of CLL, has led some expert committees to conclude that ionizing radiation exposure is not aetiologically related to CLL (BEIR-V, 1990; BEIR-VI, 1999; UNSCEAR, 2000). However, recent reports have pointed out the biological, epidemiological and methodological difficulties that have hampered efforts to assess whether ionizing radiation is related to CLL (Richardson *et al*, 2005; Schubauer-Berigan *et al*, 2007; Silver *et al*, 2007). The very low background incidence of CLL in Asian general populations has precluded a quantitative dose-response evaluation for CLL in the Japanese atomic bomb survivors (Preston *et al*, 1994, 2004), the primary radiation-exposed population employed as a basis for establishing radiation protection measures. The rarity of CLL results in a relatively small number of cases even in large radiation-exposed populations in western countries (Silver *et al*, 2007); studies of such populations may be limited further when considering the distribution of cases with respect to exposure. Many epidemiological studies of radiation in relation to CLL mortality are based on death certificates, which often lack specification of leukaemia subtype (Hall *et al*, 1992; Darby *et al*, 1994; Blettner *et al*, 2002) or combine CLL with other forms of leukaemia and lymphoma (Muirhead *et al*, 2003), thus preventing estimation of radiation-related risks of CLL. In addition, patients with CLL often die of unrelated causes, including second cancers, and CLL may not be listed on the death certificate of such patients (Richardson *et al*, 2005). Other difficulties relate to epidemiological study design, including inadequate length of follow-up or insufficient lagging of exposure to account for a protracted induction and latency period (Richardson *et al*, 2005; Schubauer-Berigan *et al*, 2007; Silver *et al*, 2007), even in nationwide or international, multi-country studies with large population size and person-years of follow-up (Boice *et al*, 1985, 1987; Curtis *et al*, 1989, 1994). Some epidemiological studies present only a global description of their findings or report the number of CLL cases, but do not report risk estimates or quantify dose-response for CLL (Smith & Doll, 1982; Hall & Holm, 1995; Shilnikova *et al*, 2003). In this issue, the results of a nested case-control mortality study of CLL within a large cohort of US nuclear workers are described, and the findings are compared with results from other studies of CLL in radiation-exposed populations (Schubauer-Berigan *et al*, 2007).

The epidemiological literature on non-ionizing radiation is more limited than that for ionizing radiation (Portier & Wolfe, 1998; Ahlbom *et al*, 2001; Schubauer-Berigan *et al*, 2007). Comprehensive assessments of health effects from exposure to power-frequency electric and magnetic field exposures have concluded that there is limited evidence of a relationship with CLL (Portier & Wolfe, 1998; Ahlbom *et al*, 2001). These conclusions are largely based on two occupational studies with small numbers of highly exposed workers (Floderus *et al*, 1994; Theriault *et al*, 1994), a third investigation that examined both occupational and residential exposures (Feychting *et al*, 1997), and a meta-analysis of 38 studies employing job-title as the primary exposure measure (Kheifets *et al*, 1997). More recently, a study in Norway found a non-significant threefold excess risk of CLL among adults living near high power lines where residential exposures were ≥0·2 μT (Tynes & Haldorsen, 2003). The relationship of radiofrequency exposures with risk of CLL has not been studied. The only investigation of ultraviolet radiation and CLL found protective effects and an

inverse dose-response trend for several important measures of sun exposure, including the number of sunburns by 20 years of age, the number of times spent sunbathing, and the number of vacations in sunny geographic regions (Smedby *et al*, 2005).

Chemical exposures. Leukaemia mortality has been evaluated in a large number of occupational cohorts (Linet *et al*, 2006), but data are limited on the relation of specific chemical exposures with CLL and largely absent for SLL (Hartge *et al*, 2006). In this issue, Blair *et al* (2007) describe many of the same limitations noted above for studies of ionizing and non-ionizing radiation, including the rarity of CLL, the late age at onset, the grouping of CLL with other leukaemias or lymphomas, and the lack of consistency in classification. Nevertheless, these investigators (Blair *et al*, 2007) have highlighted reports of excess risks of CLL and related HLD in farmers and in other agricultural occupations (Burmeister *et al*, 1982; Blair & White, 1985; Brown *et al*, 1990; Zheng *et al*, 2002; Miligi *et al*, 2003). A few studies have linked CLL with specific agricultural chemicals (Brown *et al*, 1990; Nanni *et al*, 1996; Miligi *et al*, 2003), although most studies have not evaluated specific chemical exposures (Blair *et al*, 2007). Excesses of lymphocytic leukaemia (Wolf *et al*, 1981) and NHL (Kogevinas *et al*, 1998) have been reported in a few studies of rubber workers and in petroleum workers (Glass *et al*, 2003); however, a meta-analysis of CLL among petroleum workers found little evidence of a relationship (Raabe & Wong, 1996). Further details are provided in the paper by Blair *et al* (2007).

Medical conditions and treatments. Most epidemiological studies investigating the role of medical conditions and risk of CLL have evaluated autoimmune disorders and generally have found no consistent evidence of a relationship with CLL (Linet *et al*, 1986; Rosenblatt *et al*, 1991; Landgren *et al*, 2006). A few studies examining allergic disorders or desensitization vaccinations and CLL risk have also found no clear association (Rosenblatt *et al*, 1991; Doody *et al*, 1992) or a modest protective effect (Linet *et al*, 1986). A small number of investigations have assessed the relationship between a history of transfusions and CLL and/or SLL, but the results have been inconsistent (Adami *et al*, 1997; Cerhan *et al*, 2001).

Recent studies from Scandinavia (Landgren *et al*, 2007b) and the US (Landgren *et al*, 2007a) suggest that occurrence of one or more episodes of pneumonia within 5 years of the diagnosis of CLL might serve as a potential trigger for CLL development, although it is possible that pneumonia could be a consequence of immune deficiency as an early, prediagnostic manifestation of CLL. It is noteworthy, however, that both studies (Landgren *et al*, 2007a,b) found a reduced risk of CLL among individuals with a personal history of chronic non-rheumatic valvular heart disease or chronic rheumatic heart disease, both disorders for which patients receive antibiotic prophylaxis. The rarity of CLL, the methodological shortcomings of the case-control study design for studying cancer risks associated with infectious diseases, the indolent nature of CLL and the associated immune dysfunction, together with the long latency between initial exposure and diagnosis complicate efforts to assess risk of CLL in relation to infectious organisms.

Lifestyle factors. The carcinogenicity of tobacco smoke has been recognized for decades, but it was not until 1986 that smoking was first linked with leukaemia (Austin & Cole, 1986). Smoking has most consistently been associated with moderate increases of acute myeloid leukaemia (Linet *et al*, 2006). A few cohort studies (Kinlen & Rogot, 1988; Garfinkel & Boffetta, 1990; Linet *et al*, 1991), but not all (Friedman, 1993; Adami *et al*, 1998), and some case-control studies (Brown *et al*, 1990), but not all (Stagnaro *et al*, 2001; Schollkopf *et al*, 2005), have shown an association of smoking with CLL. A pooled analysis of nine case-control studies generally showed no overall increase in risk for cigarette smoking and CLL; however, the investigators found a significant trend with increasing duration of smoking and the highest risk of CLL, albeit not statistically significant, was observed in smokers in the category with greatest number of pack-years smoked (Morton *et al*, 2005).

Increased risk of HLD has been associated with employment in cosmetology in a few studies, but CLL has generally not been associated with personal use of hair dyes in most cohort studies (Grodstein *et al*, 1994; Thun *et al*, 1994; Altekruse *et al*, 1999) or case-control studies (Zahm *et al*, 1992), with some exceptions (Markovic-Denic *et al*, 1995; Benavente *et al*, 2005; Miligi *et al*, 2005). A recent meta-analysis estimated a non-significant 40% increase in risk for CLL with hair dye use (Takkouche *et al*, 2005).

Few studies have investigated body mass index and CLL risk separately from other leukaemias or lymphomas, and there is little evidence of a relationship (Ross *et al*, 2004; Chang *et al*, 2005). There is also very little information on the possible role of physical activity or diet and risk of CLL (Cerhan *et al*, 2002).

Genetic factors. Based on findings reported during the past 60 years, a family history of CLL or other HLD is one of the strongest risk factors for development of CLL (Videbaek, 1947; Gunz *et al*, 1975; Linet *et al*, 1989; Goldin *et al*, 2004). Studies of CLL in twins (Gunz & Dameshek, 1957; Brok-Simoni *et al*, 1987), multiple siblings (Schweitzer *et al*, 1973; Fernhout *et al*, 1997), and multiple generations (Fraumeni *et al*, 1969; Gunz *et al*, 1975) are an established approach to characterizing genetic associations. Comparison of occurrence of specific cancers in monozygotic and dizygotic twins (Morley & Dwyer, 2005; Nystad *et al*, 2005), investigations of multi-generation families with several affected members (Lynch *et al*, 1976; Hemminki *et al*, 2001), and newer epidemiological study designs and analytical methods (Kraft & Thomas, 2004; Havill & Dyer, 2005; Kraft *et al*, 2007) can clarify the relative contributions of genetics and environment to disease aetiology. The paper by Caporaso *et al* (2007) in this issue reviews key aspects of the genetics of CLL.

Key questions and recommendations

Key questions for advancing understanding of CLL aetiology

How can studies of pathogenesis or prognostic factors contribute to our understanding of CLL aetiology? Clues about aetiology are suggested by our growing understanding of possible inducing factors, the origin of CLL from antigen-stimulated mature B-cells, recognition of the structural similarity of B-cell receptors among groups of patients, and the mechanisms by which lymphocytes with polyreactive B-cell receptors can evolve into clones of monoclonal B-cells. The structural similarities in antigen-binding receptors in CLL patients, in contrast with the broad diversity of these receptors in healthy persons (Stevenson & Caligaris-Cappio, 2004; Widhopf *et al*, 2004), may be an avenue for epidemiological exploration. The striking structural similarities in antigen-binding receptors among some patients with CLL suggest that a limited set of antigens (perhaps those associated with specific infections or certain chemical exposures) may provoke the clonal expansion of B-cells (Chiorazzi *et al*, 2005). Epidemiological investigations also could evaluate potential aetiological differences within CLL subgroups with distinct clinical or prognostic features defined according to molecular or genetic abnormalities.

What factors impede epidemiological studies of descriptive patterns and international comparisons of incidence rates and trends for CLL? The long-standing problems with classification of CLL and other HLD have been substantially reduced by advances in our understanding of normal B- and T-cell differentiation and of underlying factors that may serve as initiators or promoters of CLL. Adoption of the internationally recognized and reproducible WHO classification is a major step forward. Nevertheless, it is likely that this classification will continue to evolve with further advances in the understanding of the pathogenesis of CLL, including elucidation of a potential precursor condition, identification of aetiological factors, and further clarification of the inter-relationships of CLL with other HLD. Until the delays in reporting of CLL (but not SLL) are addressed, it may be useful to continue utilizing two codes for these similar entities, realizing that CLL and SLL may not be separated consistently by pathologists because of lack of uniform definitions. As a vanguard neoplasm in the increasing trend towards outpatient diagnosis and treatment of malignancies, the under-ascertainment of CLL necessitates modifications in reporting requirements and delineation of the mechanisms by which this can be accomplished.

What are the obstacles to clarifying the role of ionizing radiation, non-ionizing radiation, and occupational and residential chemical exposures in the aetiology of CLL? Several over-arching problems contribute to our very limited understanding of CLL aetiology. First, very large studies are needed to identify statistical associations, particularly for agents that may be weakly linked to CLL. Second, the lack of clear definitions, inconsistency in the definitions used, and changes in classification schemes have impeded comparisons among populations at the same time or over time. Unfortunately, there have been few case-control studies of CLL in general populations (Linet *et al*, 1986; Rosenblatt *et al*, 1991). In addition, many occupational cohorts have not had sufficient numbers of subjects to provide stable estimates of dose-response relationships for CLL. Some important exposed cohorts have been characterized by very low rates of CLL (e.g. the Japanese atomic bomb survivors), and this information may not be generalizable to other populations with higher rates. Furthermore, most large occupational cohort studies have ascertained CLL cases using death certificates or other types of records that often preclude a separate evaluation of CLL from other HLD. A third key issue, the absence of toxicology and carcinogenicity investigations in appropriate animal models, has limited our knowledge of the leukemogenicity of specific agents, although the naturally occurring NZB mouse model and recently developed transgenic mouse models of CLL should provide new research opportunities.

How can data demonstrating differences between CLL and other forms of lymphoproliferative malignancies translate into increased understanding of aetiology? Comparison of descriptive epidemiological characteristics of the various HLD reveals some similarities, but also notable differences in incidence patterns according to age, sex and race/ethnic group (Morton *et al*, 2006). Differences in incidence rate patterns among the major categories of HLD suggest differences in aetiology. As another example, cytogenetic lesions are relatively rare in the CLL clone early in the course of the disease in contrast to the frequent occurrence of chromosomal translocations involving oncogenes in other B-cell lymphomas (Chiorazzi *et al*, 2005). Comparison of risk factor associations among the various B-cell neoplasms may provide helpful insights into the possible role of specific agents in the aetiology of CLL and may clarify reasons for differences among these disorders.

Would identification of a postulated precursor for CLL provide new opportunities for identification of leukemogenic factors in epidemiological studies? To study potential aetiological factors, it is critical to understand the timing of leukemogenesis, particularly the early window prior to the development of clinical CLL. The long latency and indolent nature of the disease complicate efforts to identify initiating agents or events. Along these lines, it would be useful to identify a CLL precursor condition with a high sensitivity and specificity for the subsequent occurrence of CLL. This precursor condition would require a clearly established and internationally agreed upon definition and, ideally, be relatively easy to diagnose using widely available technology.

Can epidemiological research clarify the relative contributions of environmental and genetic factors in CLL and MBL occurrence? Epidemiologists study different populations to assess the relative contributions of environmental and heritable factors in disease aetiology. Genetically predisposed populations and relevant study designs are described more fully above and by Caporaso *et al* (2007). Epidemiological studies comparing risk factors in native-born immigrants and subsequent generations have also traditionally been helpful in disentangling the relative contributions of environmental and genetic factors. This approach is likely to be fruitful based on studies of leukaemia carried out in Asian immigrants and first- and later-generations (Herrinton *et al*, 1996; Gale *et al*, 2000; Pan *et al*, 2002).

How can epidemiological research advance understanding of the pathogenesis and natural history of CLL and MBL? In both direct and indirect ways, epidemiological research can help to clarify pathogenesis through quantification of population variation in the occurrence of CLL and MBL, assuming that MBL is confirmed as a precursor to CLL (see Marti *et al*, 2007, this issue). Although identification of the progenitor cell and initiating lesion(s) for CLL will require further basic laboratory research and studies in animal models, the use of epidemiological studies could be guided by toxicology investigations in animals known to develop CLL to pinpoint specific chemicals and other agents (including ionizing and non-ionizing radiation) postulated to be aetiologically important. Toxicological studies could also quantify dose-response and clarify whether inconsistent associations are likely to be because of these exposures or study bias.

Specific recommendations for epidemiologic research

Classification and subtype designation of CLL/SLL. The WHO classification for HLD (Jaffe *et al*, 2001) considers CLL/SLL to be a single disease entity, but the availability of separate ICD-O-3 codes for CLL and SLL provides an opportunity to evaluate these entities separately and combined. If epidemiological data reveal that risk factors for CLL and SLL are similar, then these data would provide additional support for the decision to combine CLL/SLL into a single entity in the WHO classification. Unfortunately, accrual of large numbers of CLL and SLL cases within epidemiological studies is difficult because the WHO classification has only recently been adopted by population-based cancer registries, and CLL cases are incompletely ascertained and reporting is delayed. In addition, the designation of CLL *versus* SLL may not be uniform among pathologists.

Certain CLL subgroups (e.g. those characterized by the presence or absence of *IGHV* mutation or ZAP-70 expression status) appear to have prognostic value (Chiorazzi *et al*, 2005), while the prognostic implications of other groupings (e.g. those characterized by specific cytogenetic aberrations, heavy and light chain gene rearrangement features, or restricted specific B-cell receptors) (Dohner *et al*, 2000; Tobin *et al*, 2006) are less clear. It is not known whether these potential prognostic subgroups are aetiologically important. However, concerns about the standardization of tests for characterizing subgroups must first be resolved before the potential aetiological importance of specific subgroups can be assessed in large epidemiological studies.

Completeness of ascertainment of CLL/SLL in cancer registries. It would be advantageous for cancer registries to collect information on CLL/SLL according to subcategory (CLL *versus* SLL), including the method of diagnosis, source of diagnostic information, sites of involvement, stage and, ideally, a standardized list of baseline clinical, laboratory, molecular and genetic characteristics. There are pressing needs for additional sources of information on CLL cases diagnosed as outpatients and for special studies to quantify the level of under-ascertainment and to determine the extent to which CLL reporting might be delayed. Results from these studies will be critical to subsequent efforts to develop standardized protocols to identify completely and accurately all CLL cases diagnosed within population-based cancer registry catchment areas. Should those studies confirm that there is a significant delay in reporting of CLL, further investigation of the extent, length and time trends in delay would provide critical information for statistical correction of reported CLL incidence rates.

Studies to clarify the natural history of MBL. To identify the role of postulated environmental and genetic risk factors for CLL, an improved understanding of the natural history of CLL would be extremely helpful. A starting point for characterization of the natural history is shown in Fig 1. This construct suggests that exogenous agents may interact with specific genetic factors to induce an immune response leading to MBL. A phased approach could be used beginning with efforts to characterize MBL in clinic-based settings across populations and in family members of a large number of CLL patients and in other settings of higher risk subgroups, e.g. persons >50 years of age enrolled in health maintenance organizations. Long-term follow-up will be necessary to clarify whether MBL is a precursor condition of CLL or a precursor of a broader range of HLD or other medical conditions. Once these initial investigations have been conducted and potentially high-risk occupational (e.g. farmers) or patient populations (e.g. family members of CLL cases) have been identified, it would be important to carry out prevalence and incidence surveys of such higher-risk populations to clarify the descriptive patterns of MBL. As understanding grows of the descriptive epidemiology of MBL in high-risk populations, it may be reasonable to initiate investigations in existing selected populations that are not *a priori* identified as high-risk to provide additional insights into the natural history of MBL. Follow-up of longitudinal cohorts of healthy adults with prospective collection of blood specimens also could be helpful

for assessing the occurrence of MBL associated with CLL and other outcomes in general populations. It will be important to define the occurrence and natural history of MBL prior to embarking on analytical studies to identify risk factors for MBL.

Studies to evaluate the role of ionizing and non-ionizing radiation exposures. Reviews of the literature suggest that a small number of epidemiological studies provide some evidence of an association of CLL with ionizing radiation (Richardson *et al*, 2005; Schubauer-Berigan *et al*, 2007; Silver *et al*, 2007) and with power-frequency electric and magnetic field non-ionizing radiation exposure (Ahlbom *et al*, 2001), but key studies are unable to contribute because of very small numbers of CLL cases (e.g. the atomic bomb survivors) or lack of quantitative data. It is critically important to take the biological and clinical features of CLL into account in designing epidemiological studies, to assess risks in sufficiently large (including pooled) populations (Richardson *et al*, 2005), to identify and validate diagnoses of all incident CLL cases within a population, to study risks in relation to a wide range of radiation doses, and to conduct lifetime follow-up of key populations (as CLL often arises in the elderly) to allow for sufficient latency (Richardson *et al*, 2005; Schubauer-Berigan *et al*, 2007; Silver *et al*, 2007). Investigators pooling cohort incidence data across populations should recognize that there may be variation in the completeness of ascertainment of CLL cases and substantial delays in reporting of cases to cancer registries. The variation across populations may be even greater when pooling cohort mortality data because of the numerous difficulties with identification of CLL from death certificates.

Studies to evaluate the role of chemical exposures. The excesses of CLL in farmers, other agricultural occupations, and rubber and petroleum workers suggest that specific agrichemicals, such as chlorinated hydrocarbons (Flodin *et al*, 1988; Malone *et al*, 1989), fungicides and insecticides (Brown *et al*, 1990), carbamates and organophosphates (Nanni *et al*, 1996), triazines, amides, cyclohexames and ziram (Miligi *et al*, 2003), chemicals used by animal farmers (Amadori *et al*, 1995), solvents (Malone *et al*, 1989; Seidler *et al*, 2007), butadiene (Divine & Hartman, 2001; Graff *et al*, 2005) and possibly benzene (Glass *et al*, 2003; Smith *et al*, 2007b), should be evaluated in more detail. Similar to the recommendations for assessing radiation exposures, it is also important to incorporate strategies for lifetime follow-up of exposed cohorts to allow for long latency. Most of the methodological issues described above for pooling cohort incidence and/or mortality data on ionizing and non-ionizing radiation exposures across populations also apply to cohort data on chemical exposures.

Studies to assess whether particular infectious agents have an aetiological role in CLL. Studies are needed to evaluate new findings, such as those described by Landgren *et al* (2007a). Initially, it will be important to determine if the excess risk of pneumonia is seen in other studies and if it is associated with particular infectious agents. Potential populations to consider for these studies include those that can be evaluated using registry linkage, e.g. the US SEER-Medicare linked database, large patient populations enrolled in US health maintenance organizations, or populations in countries with national health-care systems and computerized records. In such studies, it will be important to assess latency and to have sufficient numbers of patients with long latency between infection and the onset of CLL to provide clear evidence that the infections are not an early manifestation of CLL.

Studies to evaluate lifestyle factors. The availability of cohort consortia with large numbers of subjects provides the opportunity for pooling questionnaire data across large populations to evaluate the role of common exposures, including smoking, alcohol consumption, hair dye use, body mass index, physical activity and risk of CLL.

Conclusion

Major advances in our understanding of the basic biology of CLL have resulted in a highly reproducible classification scheme for CLL and other HLD (Jaffe *et al*, 2001). The worldwide adoption of this classification system, our greater understanding of the pathobiology of CLL, along with the recent reassessment of a possible aetiological role of ionizing radiation (Richardson *et al*, 2005; Schubauer-Berigan *et al*, 2007; Silver *et al*, 2007) and certain chemical exposures (IOM, 2005; Blair *et al*, 2007), make it timely to assess these and other leads in new epidemiological studies of CLL. Importantly, the identification of MBL, if confirmed to be a CLL precursor, will facilitate aetiological studies of CLL.

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