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New Aspects in Descriptive, Etiologic, and Molecular Epidemiology of Hodgkin's Lymphoma

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Hodgkin's disease was first described in 1832 by Thomas Hodgkin (1798–1866) who published his article entitled "On some morbid appearances of the adsorbent glands and spleen," describing the post-mortem appearance of seven patients who had enlargements of lymph nodes and spleen [1]. More than 30 years later, based on some 15 additional cases, Wilks published his article entitled "Cases of enlargement of the lymphatic glands and spleen, (or, Hodgkin's disease) with remarks" which ultimately named the disease after Thomas Hodgkin [2]. In 2001, the World Health Organization (WHO) lymphoma classification system designated Hodgkin's disease to Hodgkin's lymphoma [3].

Although Hodgkin's lymphoma is a rare hematopoietic malignancy in the general population [4,5], it has drawn much attention among generations of clinicians, pathologists, and researchers deriving from its generally unusual biology and epidemiology and because it is one of the first malignancies to exhibit curative response to chemotherapy. Its symptomatic features (such as recurrent cycles of fever, night sweats, and lymphadenopathy), which at times emerge clinically like an infectious disease, and preferential targeting of young adults have influenced many clinicians and researchers to suspect an infectious cause of the malignancy.

Etiologic clues about Hodgkin's lymphoma have been suggested by the bimodal age distribution; by elevated risks in males, in individuals with higher socioeconomic status, and in smaller families; and by the occurrence of Epstein-Barr virus in Hodgkin's lymphoma tumor cells [6,7]. After the introduction of highly active antiretroviral therapy (HAART) in 1996 for HIV-infected people, AIDS non-Hodgkin's lymphoma has declined substantially; however, the incidence of Hodgkin's lymphoma has been observed to increase simultaneously [8]. In the past decade, there have been reports showing increased

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risk for Hodgkin's lymphoma among individuals who have undergone organ transplant or bone marrow transplant [9,10]. More recently, autoimmune and related conditions have drawn attention to a potential role for immune-related and inflammatory conditions in the cause and pathogenesis of the malignancy [11]. A role for genetic factors is unequivocal based on evidence from multiply affected families from case series, a twin study, a case-control study, and population-based registry studies [12–17]. Emerging data from Eastern Asia and among Chinese immigrants in North America indicate increasing incidence trends for Hodgkin's lymphoma associated with westernization, which emphasizes the importance of lifestyle and environmental risk factors even in a short-term perspective [18,19].

CLASSIFICATIONS OF HODGKIN'S LYMPHOMA

Evolving Classification Systems

Jackson and Parker were the first to propose a comprehensive classification of Hodgkin's lymphoma [20,21]. This classification was subsequently found to be clinically irrelevant, because most of the patients belonged to the granuloma subtype with a huge variation in response to therapy and outcome. In 1956, Smetana and Cohen identified a variant of granuloma characterized by sclerotic changes and a better prognosis [22]. Lukes and Butler suggested a histologic classification distinguishing six types of Hodgkin's lymphoma based on the varying degree of lymphocytic infiltration [23–25]. At the Rye symposium in 1965 the number of separate histologic groups was reduced from six to four and thereafter applied routinely for several decades because of the high reproducibility and good clinicopathologic correlations. In 1994, in light of morphologic, phenotypic, genotypic, and clinical findings, Hodgkin's lymphoma was listed in the Revised European-American Lymphoma classification and subdivided into two main types: nodular lymphocyte-predominant and classic Hodgkin's lymphoma [3,26]. Classic Hodgkin's lymphoma was further divided into four histologically and clinically defined subtypes: nodular sclerosis, mixed cellularity, lymphocyte-rich, and lymphocyte-depleted. This approach has been adopted by the most recent WHO classification of lymphomas [3], which promoted classic Hodgkin's lymphoma from a provisional to an accepted entity.

Heterogeneous Neoplastic Cells

Nodular lymphocyte-predominant and classic Hodgkin's lymphoma [3,26] share certain pathognomonic characteristics. For example, affected tissues contain only a small number of neoplastic Hodgkin's and Reed-Sternberg cells (typically less than 1%) in a background of nonneoplastic inflammatory and accessory cells [3], suggestive of a chronic inflammatory process. Several lines of evidence indicate that the neoplastic cells of Hodgkin's lymphoma originate from a germinal center or immediate postgerminal B cell that has been selected and stimulated by antigen [27–32]. Further, immunohistochemical studies have found neoplastic cells of nodular lymphocyte-predominant Hodgkin's

lymphoma (popcorn cells) to be of BCL6+/CD138− phenotype, which is typical for germinal center cells. For the classic Hodgkin's lymphoma subtype, however, the neoplastic cells (Reed-Sternberg cells) have been observed to be typically BCL6+/CD138−, but sometimes they can be BCL6−/CD138+, which suggests that classic Hodgkin's lymphoma is a heterogeneous entity, including tumors of germinal center and postgerminal center B cell origin [33–35]. In rare cases of classic Hodgkin's lymphoma, tumor cells have been observed to be derived from peripheral (postthymic) T cells [36,37].

DESCRIPTIVE EPIDEMIOLOGY

Incidence and Mortality in Western Countries

Hodgkin's lymphoma composes about 11% of all lymphomas in western countries and has a unique bimodal (sometimes trimodal) age-incidence shape (Fig. 1). It is currently estimated by the American Cancer Society that there will be about 8190 new cases (55% males) and 1070 (72% males) deaths of Hodgkin's lymphoma in the United States in 2007 [38]. Also, the United States National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) and European-based International Agency for Research on Cancer

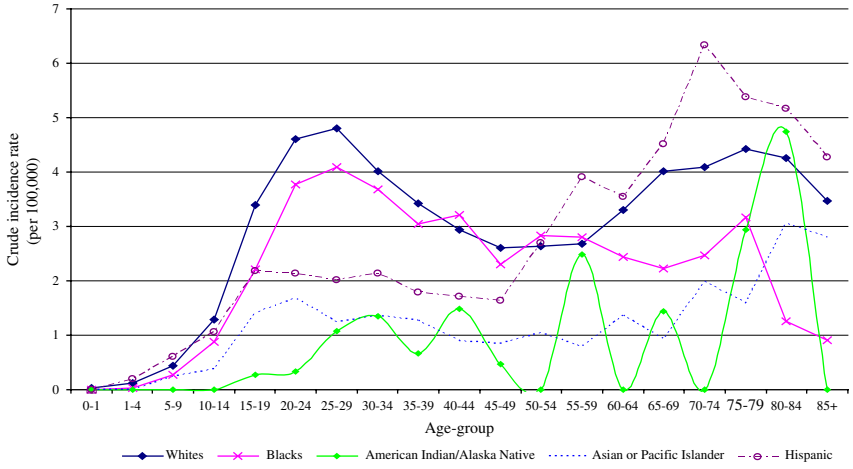

Fig. 1. Incidence of Hodgkin's lymphoma in the United States 1994–2003, by age and race. Statistics for American Indians/Alaska Natives do not include cases for the 2003 diagnosis year. Hispanic and Non-Hispanic are not mutually exclusive from White, Black, American Indian/Alaska Native, and Asian or Pacific Islander. Statistics for Hispanics and Non-Hispanics are based on NHIA and do not include cases from the Hawaii, Seattle, and Alaska Natives registries. Statistics for American Indians/Alaska Natives include cases from the Connecticut, Detroit, Iowa, New Mexico, Seattle, Utah, Atlanta and Alaska Natives registries. (*Data from* Surveillance, Epidemiology, and End Results (SEER) Program. SEER stat database: incidence—SEER13 regs public use, Nov 2005 Sub (1992–2003), National Cancer Institute, DCCPS, Surveillance Research Program, cancer Statistics branch, released April 2006, based on the November 2005 submission. Available at: http://www.seer.cancer.gov.)

population-based cancer registries have estimated the incidence of Hodgkin's lymphoma in the United States and in Europe to be around 2.3 to 3.1 per 100,000 males and 1.6 to 2.3 per 100,000 females, which underscores that Hodgkin's lymphoma is a rare malignancy in the general population [4,5]. Although the risk for developing Hodgkin's lymphoma is small (a life time risk of 0.24% for males and 0.20% for females) [5], it accounts for approximately 15% of all cancers in young adults (15 to 24 years). As to racial variation within the United States, a previous study on cancer incidence in California found the highest Hodgkin's lymphoma rates among whites, followed by African Americans and Hispanics, and the lowest incidence was observed among people of Asian descent [39]. This pattern is consistent with currently available data from the SEER database (see Fig. 1) [5].

The introduction of modern staging procedures and advances in radiotherapy and chemotherapy have significantly contributed to improved survival of patients who have Hodgkin's lymphoma over the past decades [40]. Clinical trials have observed long-term failure-free survival of 60% to 70% among patients treated with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD)–based therapies [41,42]. The German Hodgkin's Study Group has reported further improved outcomes using their dose-escalated BEACOPP regimen (including cyclophosphamide, doxorubicin, etoposide, procarbazine, prednisone, vincristine, and bleomycin) developed for patients who have advanced-stage Hodgkin's lymphoma [43]. Consistent with results from clinical trials, data from 2000 to 2003 in the population-based SEER database reveal mortality rates for patients who have Hodgkin's lymphoma of 0.4 per 100,000 and 0.3 per 100,000 for males and females, respectively [5]. If one restricts the estimates to patients who are 65 years or older, the mortality rates are 2.1 per 100,000 (males) and 1.4 per 100,000 (females). By using 5-year relative survival rates as the measure of outcome the same pattern can be seen: the 5-year relative survival rates for all Hodgkin's lymphoma is about 85%, whereas the corresponding relative survival rate for older patients (65 years or older) is only 53% [5]. The outcomes of elderly (>50–60 years) patients still remain unsatisfactory, however, with inferior complete remission rates and overall survival [44–46]. Because older patients generally are not included in clinical trials the information on this topic is sparse. Population-based data from Scandinavia show that the 5-year overall survival for younger patients (diagnosed younger than age 50 years) increased from about 55% to 90% between the two calendar periods 1926 to 1955 and 1972 to 1994, whereas the corresponding improvement for patients diagnosed at 50 years or older improved from 20% to 50% during the same calendar periods [47,48]. Currently the underlying mechanisms for the clinically well-known poor prognosis of older patients who have Hodgkin's lymphoma treated with chemotherapy [49–53] remain unclear. Hodgkin's lymphoma in older patients is clinically more aggressive in that anemia, increased erythrocyte sedimentation rate, and B symptoms are significantly more frequent at diagnosis among the elderly [50,54], which supports the hypothesis of age-related disease

differences in Hodgkin's lymphoma. Alternatively, aging itself and associated factors (such as increased comorbidity [55], reduced tolerability of conventional therapy [49,56], more severe toxicity and treatment-related deaths [57,58], and poorer outcome after relapse [59]) may contribute to the worse prognosis for elderly patients. Future research is needed to explore disease mechanisms by age for patients who have Hodgkin's lymphoma. Clinically, more accurate markers of outcome in combination with less toxic novel therapies are needed [44–46].

International Variation and Westernization

The incidence of Hodgkin's lymphoma has been found to vary between westernized countries versus economically disadvantaged countries (Fig. 2). In the early 1970s, three epidemiologic patterns were described by Correa and O'Conor: type I in developing countries (a first incidence peak in male children and a second peak in older age around 50 years, with a predominance of histopathologic subtypes mixed cellularity and lymphocyte-depleted); type II in rural areas of developed countries (an intermediate pattern with high male childhood incidence and a second decade peak among females); type III in developed urbanized countries (a bimodal age distribution with a pronounced peak in young adults experiencing nodular sclerosis as the most frequent histopathologic subtype, and a continuously rising incidence older than 40 years) [60]. Correa and O'Conor [60] suggested that the observed variation in international patterns of disease reflected differences in economic development (ie, correlated for example with the level of public hygiene). More recent data from the mid-1990s have shown that the incidence rates for young adults have increased in less developed countries while remaining static in western countries [61]. A recent study from Japan, where historically Hodgkin's lymphoma has been rare before the age of 50, reported increasing incidence of Hodgkin's lymphoma in recent decades [62]. The Cancer registry in Singapore has observed (in parallel with data from Hong Kong) that local rates of non-Hodgkin's lymphoma (1998–2002, n = 1170) are the highest in Asia and the incidence has steadily increased over the past four decades [19], consistent with the well-documented rising trends in western societies the past almost half century [63]. Between 1998 and 2002 the age-standardized rates for males and female were 8.2 and 5.0 per 100,000, respectively. During the period 1993–1997 the corresponding rates were 7.5 and 4.4 per 100,000 and for the period 1968–1972 they were 3.1 and 1.9, respectively. For Hodgkin's lymphoma, the number of cases between 1998 and 2002 is small (n = 122), making interpretation of the time trend difficult. There is evidence of an upward trend of the malignancy over the past decade, however [19].

In a recent study on incidence trends for Hodgkin's lymphoma among immigrants of Chinese descent in British Columbia, Canada, Au and colleagues [18] found the incidence of Hodgkin's lymphoma among Chinese immigrants to be significantly lower than expected from the British Columbia background population (standardized incidence ratio [SIR] = 0.34; $P < .0001$). At the same

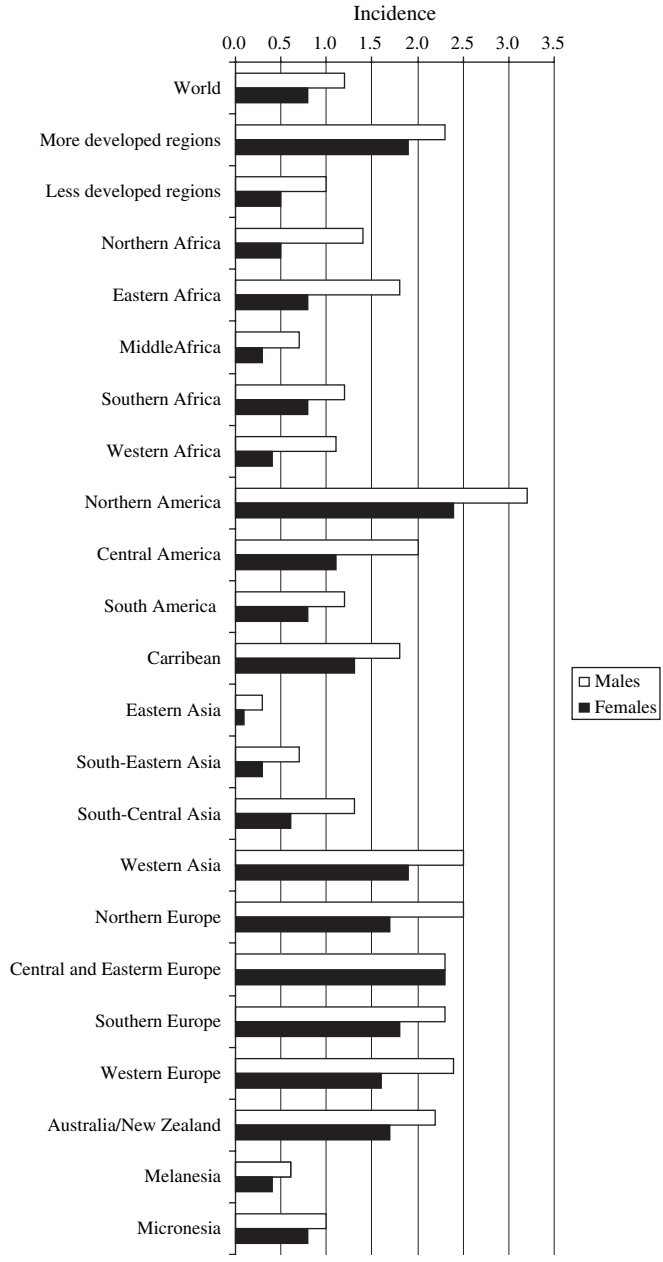

Fig. 2. Global incidence of Hodgkin's lymphoma 2002, by sex and region. Age-standardized rates per 100,000 person-years (world 2000 population). However, although the populations of the different countries are those estimated for the middle of 2002, the disease rates are not those for the year 2002, but from the most recent data available, generally 2–5 years earlier. The numbers of cases are computed by multiplying the estimated rates by the year 2002 population estimates for the corresponding country.The GLOBOCAN 2002 database provides estimates for the year 2002. (*Data from* Ferlay J, Bray F, Pisani P, et al. GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide. IARC CancerBase No. 5. version 2.0. Lyon: IARCPress; 2004.)

time, however, the incidence was significantly higher than that expected by extrapolating from the Hong Kong Chinese population (SIR = 2.81; $P < .0001$) [18]. The difference was mainly accounted for by young immigrants diagnosed with nodular sclerosis Hodgkin's lymphoma subtype. Although that study was restricted in size, it supports the hypothesis of a role for genetic, lifestyle, and environmental factors in the pathogenesis of Hodgkin's lymphoma. The results indicate that environmental and lifestyle factors can exert their influence over a relatively short period of time. Taken together, there is need for studies designed to quantify incidence trends for lymphomas in countries under the influence of westernization. Such results might provide opportunities to generate hypotheses regarding risk factors for the development of lymphomas and also are useful measures for health care planners who are responsible for future allocation of health care resources in these regions.

Secondary Tumors and Late Cardiovascular Disease

Developments in modern therapy have dramatically improved survival over the past decades for patients who have Hodgkin's lymphoma. Unfortunately, the improved outcome has been accompanied by long-term toxicity, such as elevated risk for second primary malignancies [64,65], cardiovascular disease [66], and infections [66,67]. In fact, second malignant neoplasms now are the leading cause of death among long-term survivors of Hodgkin's lymphoma [68], with breast cancer being the most common solid tumor among women [69]. The most pronounced risk for breast cancer has been found among women diagnosed with Hodgkin's lymphoma at age 30 years or younger [69–71] and is strongly associated with chest radiotherapy for Hodgkin's lymphoma. Risk has been reported to increase up to eightfold with increasing given radiation dose [69,71,72]. Other reported second cancers include acute nonlymphocytic leukemia, non-Hodgkin's lymphoma, lung cancer, stomach cancer, and melanoma [73]. Similar to the pattern of elevated risk for breast cancer, risks for other second cancer sites are highest among patients treated for Hodgkin's lymphoma at younger ages. Also, most solid tumors have been found to start within or at the edge of the irradiated field. Elevated radiation-related risks for second tumors have been found to increase even 20 to 30 years following therapy [73]. Finally, several studies have reported increased mortality of cardiac disease after mediastinal radiotherapy for Hodgkin's lymphoma [66,67]. Anthracycline chemotherapy significantly adds to the elevated risks of congestive heart failure (HR = 2.8) and valvular disorders (HR = 2.1) from mediastinal radiotherapy [74].

ETIOLOGIC AND MOLECULAR EPIDEMIOLOGY

Epstein-Barr Virus and Other Candidate Viruses

Over the past decades Epstein-Barr virus (EBV) has been the major candidate for an infectious agent causing Hodgkin's lymphoma. Previous studies have reported that individuals who have a personal history of infectious mononucleosis have an elevated risk for developing Hodgkin's lymphoma. The elevated risk for

Hodgkin's lymphoma has been found to be greater among people infected at older ages and weaker with time since infection [75]. Hypothetically, the observed association with infectious mononucleosis could reflect higher socioeconomic status resulting in relatively late infections with EBV. Based on Scandinavian data, however, there is no elevated risk for Hodgkin's lymphoma among first-degree relatives of patients who have infectious mononucleosis, strengthening the case for increased risk with infectious mononucleosis itself [75].

Previous studies investigating serum from patients who have Hodgkin's lymphoma have reported altered EBV antibody patterns. Typically, patients who have Hodgkin's lymphoma have higher mean antibody titers to EBV viral capsid antigen consistent with prior infection. Also, there is serologic evidence of elevated antibodies to early antigen and Epstein-Barr nuclear antigen among individuals subsequently diagnosed with Hodgkin's lymphoma [76].

Detection of the EBV genome has been reported in malignant cells of about one third to one half of the Hodgkin's lymphoma cases [76]. Almost all studies have demonstrated that EBV is more likely to be associated with the mixed cellularity subtype than with the nodular sclerosis subtype. The nodular lymphocyte-predominant subtype is not associated with EBV infection. The association of EBV with Hodgkin's lymphoma is strongest in children and the elderly and it is also more frequent in males than in females. The frequency of EBV association is higher in Asian and Central/Middle American countries than in the United States and Europe [77]. In situ hybridization and immunohistochemistry studies of affected tissues have demonstrated that EBV is localized to neoplastic Reed-Sternberg cells, which express EBV latent genes. Southern blot analysis of the fusion pattern of the EBV terminal repeat have shown that EBV in Reed-Sternberg cells is clonal. This evidence provides plausible evidence for the role of EBV in the pathogenesis of Hodgkin's lymphoma. EBV genome has only been found within the tumor in about 20% to 40% of patients who have Hodgkin's lymphoma with a prior diagnosis of infectious mononucleosis [78,79] and in around 30% to 40% of young adult patients overall [80]. Somewhat unexpected in relation to these findings, the association between infectious mononucleosis and Hodgkin's lymphoma has been found to be strongest for EBV-positive (versus EBV-negative) tumors [78,80]. One explanation is that EBV has been proposed to be the cause in patients who do not have viral genomic material within the tumor by way of a hit-and-run mechanism. Recent studies have not found evidence to support that hypothesis, however [81]. Based on the available evidence, the relationship between EBV and Hodgkin's lymphoma is plausible but unproven.

Several other viruses (such as cytomegalovirus, human herpesviruses 6, 7, and 8, polyoma viruses JC and BK, SV40, lymphotropic papovavirus, adenoviruses, human T-lymphotropic virus 1, and measles virus) have been examined as potential candidates or cofactors for involvement in Hodgkin's lymphoma. There is no consistent evidence indicating that these viruses are important in the cause of Hodgkin's lymphoma [82]. The risk for Hodgkin's lymphoma has been found to be elevated among people infected with HIV

[83]. Further, it has been observed that HIV-associated patients who have Hodgkin's lymphoma are more likely to be of mixed-cellularity or lymphocyte-depletion subtype and 80% to 100% of the cases have been reported to be EBV positive [84]. In a recent study investigating lymphoma trends in relation to HAART therapy, it was found that the dramatic decrease of non-Hodgkin's lymphoma has been paralleled by an increase of Hodgkin's lymphoma [8]. Currently, the underlying mechanisms for that observation remain unknown.

Autoimmunity and Hodgkin's Lymphoma

Autoimmune diseases are characterized by dysregulated lymphocyte reactivity against self-antigens and the production of autoantibodies, leading to damage of the targeted tissues, such as joints or skin [85]. Previous studies have shown that there is an increased risk for mainly non-Hodgkin's lymphoma subsequent to autoimmune conditions, including rheumatoid arthritis, Sjögren syndrome, and systemic lupus erythematosus [86–97]. Recent studies focusing on underlying pathophysiologic mechanisms related to lymphomagenesis have provided new evidence establishing differences in the risk for non-Hodgkin's lymphoma development associated with various autoimmune disorders [98]. A recent study investigated the association between a wide range of autoimmune conditions and subsequent risk for Hodgkin's lymphoma [11]. Elevated risk for Hodgkin's lymphoma was found for personal histories of several autoimmune conditions, including rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis, and immune thrombocytopenic purpura. Also, a significant increased risk for Hodgkin's lymphoma was associated with family histories of sarcoidosis and ulcerative colitis. The association between personal and family history of sarcoidosis and a statistically significant increased risk for Hodgkin's lymphoma suggests shared susceptibility for these conditions.

Transplant and Hodgkin's Lymphoma

Allogeneic bone marrow transplantation is associated with an elevated risk for developing posttransplant lymphoproliferative disorders (PTLD). Although Hodgkin's lymphoma after transplantation is rare, an elevated risk has been reported [10]. Five of six assessable cases contained EBV genome. Differences from posttransplant lymphoproliferative disease after bone marrow transplantation were later onset (>2.5 years) and lack of association with established risk factors (such as T-cell depletion and human leukocyte antigen disparity). As pointed out by Rowlings and colleagues [10], the long latency of Hodgkin's lymphoma after transplant and the lack of association with risk factors for PTLD is remarkable and should be explored further for possible insights into pathogenesis.

Previous studies of solid organ transplant patients have not generally found an elevated risk for Hodgkin's lymphoma. The Israel Penn Transplant Tumor Registry lists Hodgkin's lymphoma as the lymphoid malignancy in 2.5% (31 cases) among 1252 diseases following solid organ transplant [99]. EBV nuclear material has been demonstrated in some of the cases of Hodgkin's lymphoma following transplantation [100,101].

Genetic Factors

The importance of genetic factors in Hodgkin's lymphoma is indicated by reports of multiply affected families from case series, a twin study, a case-control study, and population-based registry studies performed in Utah, Denmark, Israel, and Sweden [12–17]. Our group recently analyzed data from registries in Scandinavia and found significant familial aggregation of Hodgkin's lymphoma (relative risk = 3.1) and other lymphoproliferative tumors [13]. Relative risks were higher in males compared with females, and in siblings of patients compared with parents and offspring. Relatives of earlier-onset patients were at higher risk for Hodgkin's lymphoma and for all lymphoproliferative tumors and were also at higher risk for developing early onset tumors themselves.

Currently, it is not known whether (or how) extrinsic risk factors interact with genetic susceptibility. Identifying inherited susceptibility genes is an important step toward defining the pathways leading to development of Hodgkin's lymphoma and understanding its complex etiology. Until recently, there have been no comprehensive searches of the genome for Hodgkin's lymphoma genes, largely because of the difficulty in assembling informative samples. In 2005, a study including 44 informative high-risk Hodgkin's lymphoma families was conducted. In that study, whole-genome scanning was applied using densely spaced microsatellite markers to localize susceptibility genes [102]. The strongest linkage finding was on chromosome 4p near the marker D4S394. The logarithm of odds score calculated by Genehunter Plus was 2.6 (nominal $P = .0002$) when both Hodgkin's lymphoma and non-Hodgkin's lymphoma individuals were considered affected. Other locations suggestive of linkage were found on chromosomes 2 and 11. The findings from this investigation are consistent with recessive inheritance. These results are the first step in the discovery of germ line susceptibility genes and delineation of the pathways involved in development of Hodgkin's lymphoma. Future work is needed to better define pathways and to determine their interactions with environmental factors.

Other Factors

Based on the shape of the incidence curve for Hodgkin's lymphoma by age and gender, Glaser proposed in the mid-1990s that that childbearing potentially could be protective against Hodgkin's lymphoma in adult women [103]. Results from Norwegian studies have supported this hypothesis [104,105]; however, the difference in the shape of the incidence curves between the sexes was not seen in England and Wales [106].

Prior studies examining occupational exposures and subsequent cancer risk have reported on Hodgkin's lymphoma risk. The results on Hodgkin's lymphoma risk in relation to exposure to wood and wood dust and chemicals are inconsistent and based on small numbers. Phenoxy herbicides and chlorophenols have also been investigated but, again, there has not been consistent evidence of a causal association [107]. There is no evidence of an association of ionizing radiation with risk for Hodgkin's lymphoma. Some studies have

found elevated risk for Hodgkin's lymphomas following tonsillectomy; however, the results are inconsistent.

FUTURE RESEARCH

Continued studies are needed to clarify the roles of EBV, HIV, and autoimmunity in the etiology and pathogenesis of Hodgkin's lymphoma. Future work also is needed to better define germ line susceptibility genes, to delineate pathways, and to determine their interactions with environmental factors. Observed increasing incidence trends for Hodgkin's lymphoma and their possible association with westernization should also be followed up.

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