Current Insight on Trends, Causes, and Mechanisms of Hodgkin's Lymphoma

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Abstract: Hodgkin's lymphoma (HL) has a unique and distinct history, epidemiology, treatment, and biology. A viral agent or infectious agent has long been considered as the etiologic agent and Epstein-Barr virus is the main candidate for the infectious agent causing HL; however, Epstein-Barr virus genome is found within the tumor in only about 20% to 40% of HL cases with a prior diagnosis of infectious mononucleosis. Recently, autoimmune and related conditions have drawn attention to a potential role for immune-related and inflammatory conditions in the etiology and pathogenesis of the malignancy. Evidence from multiply-affected families, a twin study, a case-control study, and population-based registry studies implicate genetic factors. Data from Eastern Asia and among Chinese immigrants in North America indicate increasing incidence trends for HL being associated with westernization. These results emphasize an interaction between environmental and genetic risk factors in HL.

Key Words: epidemiology, Hodgkin's lymphoma, etiology

(*Cancer J* 2009;15: 117–123)

In 1832 Thomas Hodgkin (1798–1866) published his article entitled "On some morbid appearances of the adsorbent glands and spleen," describing the postmortem appearance of 7 patients with lymph node and spleen enlargements.[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 lymphoma classification system designated Hodgkin (sic) disease to Hodgkin (sic) lymphoma.[3]

Hodgkin's lymphoma (HL)[4,5] has drawn attention from clinicians, pathologists, and researchers in part due to its generally unusual biology and epidemiology, but also 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 HL have been suggested by the bimodal age distribution with one peak occurring in the third decade of life and a second peak after age 50 years; by elevated risks in men, in individuals with higher socioeconomic status and in smaller families; and by the occurrence of Epstein-Barr virus (EBV) in HL tumor cells.[6,7] Interestingly, after the introduction of highly active antiretroviral therapy in 1996 for HIV-infected persons, AIDS non-HL (NHL) has declined substantially; however, the incidence of HL has been observed to increase simultaneously.[8] In the past decade, increased risk of HL among individuals who have undergone organ transplant or bone marrow transplant[9,10] has been reported. More recently, autoimmune and related conditions have drawn attention to a potential role for immune-related and inflammatory conditions in the etiology 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 HL 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

Classification Systems

Jackson and Parker[20] and Harris[21] were the first to propose a comprehensive classification of HL. However, 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[22] identified a variant of granuloma characterized by sclerotic changes and a better prognosis. Lukes and Butler suggested a histologic classification distinguishing 6 types of HL 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 6 to 4 and thereafter applied routinely for several decades because of the high reproducibility and good clinicopathological correlations. In 1994, in the light of morphologic, phenotypic, genotypic, and clinical findings, HL was listed in the Revised European-American Lymphoma classification and subdivided into 2 main types: nodular lymphocyte predominant and classic HL.[3,26] Classic HL was further divided into 4 histologically and clinically defined subtypes: nodular sclerosis, mixed cellularity, lymphocyte rich, and lymphocyte depleted. This approach has been adopted by the most recent World Health Organization classification of lymphomas,[3] which promoted classic HL from a provisional to an accepted entity.

Origin of Neoplastic Cells

Nodular lymphocyte predominant and classic HL[3,26] share certain pathognomonic characteristics. For example, affected tissues contain only small number of neoplastic Hodgkin's and Reed-Sternberg cells (typically less than 1%) in a background of non-neoplastic inflammatory and accessory cells,[3] suggestive of a chronic inflammatory process. Several lines of evidence indicate that

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Supported by the Intramural Research Program of the National Institutes of Health, National Cancer Institute.

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ISSN: 1528-9117/09/1502-0117

the neoplastic cells of HL originate from a germinal center or immediate postgerminal B-cell which has been selected and stimulated by antigen.[27–32] Furthermore, immunohistochemical studies have found neoplastic cells of nodular lymphocyte predominant HL (popcorn cells) to be of $BCL6^{+}/CD138^{-}$ phenotype which is typical for germinal center cells. For the classic HL 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 HL is a heterogeneous entity including both tumors of germinal center and postgerminal center B-cell origin.[33–35] In rare cases of classic HL, tumor cells have been observed to be derived from peripheral (post-thymic) T-cells.[36,37]

DESCRIPTIVE EPIDEMIOLOGY

Incidence and Mortality in Western Countries

HL comprises about 30% 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 8220 new cases (55% men) and 1350 (72% men) deaths of HL in the United States in 2008.[38] Also, the United States National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) and European-based International Agency for Research on Cancer population-based cancer registries have estimated the incidence of HL in the United States and in Europe to be around 2.3 to 3.1 per 100,000 men and 1.6 to 2.3 per 100,000 women, which underscores the fact that HL is a rare malignancy in the general population.[4,5] Although the risk of developing HL is small (a life time risk of 0.24% for men and 0.20% for women),[5] it accounts for approximately 15% of all cancers in young adult ages (15–24 years). In terms of racial variation within the United States, a previous study on cancer incidence in California found the highest HL rates among whites, followed by African Americans and Hispanics, and the lowest incidence was observed among persons of Asian descent.[39] This pattern is consistent with currently available data from the SEER database (Fig. 1).[5]

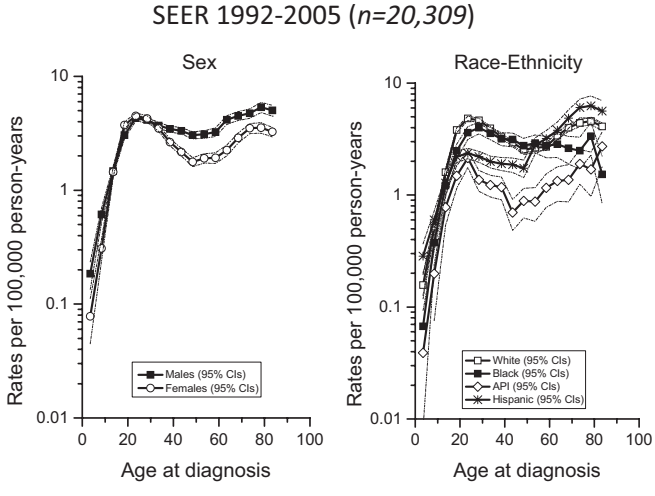

FIGURE 1. Age-specific incidence rates with 95% confidence intervals in the National Cancer Institute's SEER Database for Hodgkin's lymphoma by sex and Race-Ethnicity. API, Asian or Pacific Islander; Hispanic races are not mutually exclusive from white, black, API. Statistics for Hispanics are based on the NHIA (NAACCR Hispanic Identification Algorithm) and exclude cases from the Alaska Native Registry and Kentucky.[115,116]

The introduction of modern staging procedures and advances in both radiotherapy and chemotherapy have significantly contributed to improved survival of patients with HL 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-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 with advanced stage HL.[43] Consistent with results from clinical trials, data from 2000 to 2003 in the population-based SEER database reveal mortality rates for HL patients of 0.4 per 100,000 and 0.3 per 100,000 for men and women, respectively.[5] However, if one restricts the estimates to patients that are 65 years or older, the mortality rates are 2.1 per 100,000 (men) and 1.4 per 100,000 (women). 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 HL is about 85% while the corresponding relative survival rate for older patients (65 years or older) is only 53%.[5] Thus, the outcomes of elderly (>50–60 years) patients still remain unsatisfactory, 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. However, population-based data from Scandinavia show that the 5-year overall survival for younger patients (diagnosed below the age of 50) increased from about 55% to 90% between the 2 calendar periods 1926–1955 and 1972–1994; while 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 HL patients treated with chemotherapy[49–53] remain unclear. HL in older patients is clinically more aggressive in that anemia, increased erythrocyte sedimentation rate, advanced stage, and B-symptoms are significantly more frequent at diagnosis among the elderly,[50,54] which supports the hypothesis of age-related disease differences in HL. 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 of elderly patients. Future research is needed to explore disease mechanisms for HL patients by age.[60] Clinically, more accurate markers of outcome in combination with less toxic novel therapies are needed.[44–46]

International Variation and Westernization

The incidence of HL varies between westernized countries versus economically disadvantaged countries (Fig. 2). In the early 1970s, 3 epidemiological 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 women); 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 above 40 years).[61] Correa and O'Conor[61] 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

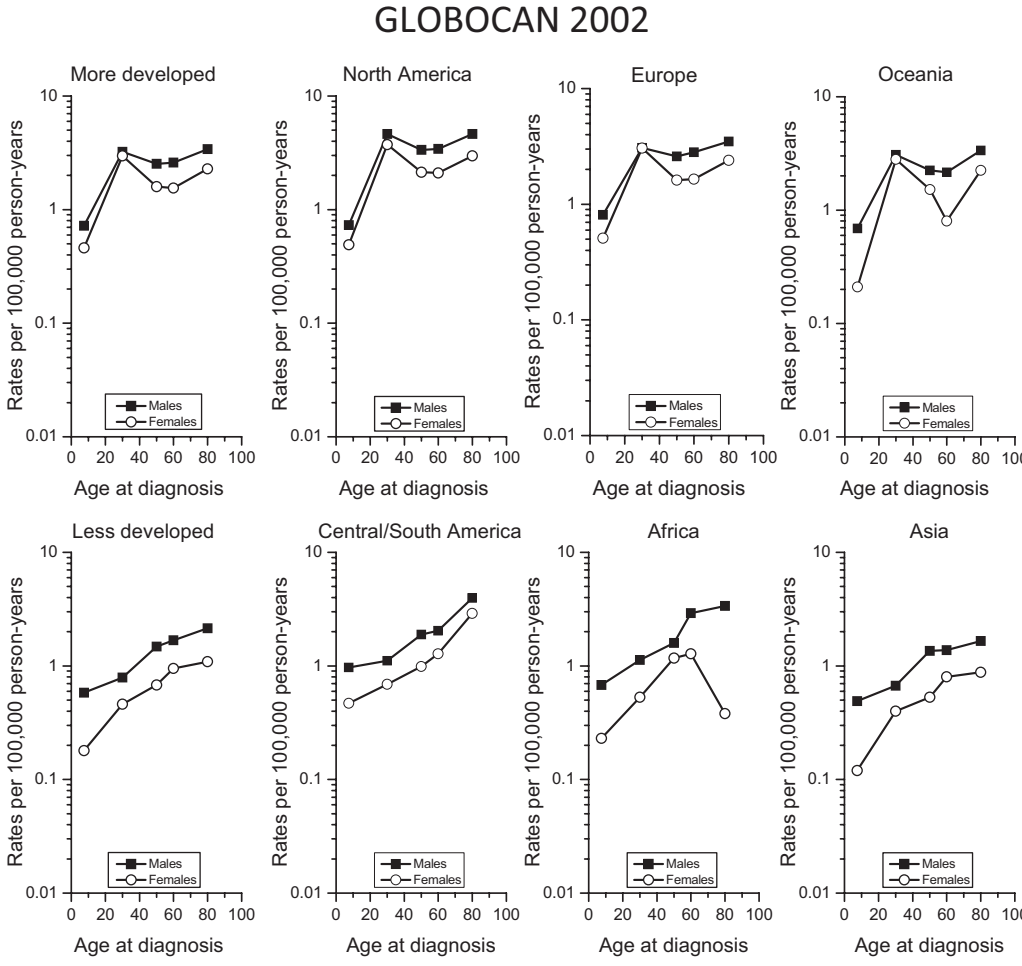

FIGURE 2. Age-specific incidence rates in GLOBOCAN 2002 for Hodgkin's lymphoma by sex and geographic regions. More developed regions have been calculated as the population-weighted average of Northern America, Japan, Eastern Europe, Northern Europe, Southern Europe, Western Europe, and Ocean (Australia/New Zealand). Less developed regions have been calculated as the population-weighted average of Eastern Africa, Middle Africa, Northern Africa, Southern Africa, Western Africa, Caribbean, Central America, South America, Eastern Asia (less Japan), South Eastern Asia, South Central Asia, Western Asia, Melanesia, Micronesia, and Polynesia.[117]

developed countries while remaining static in western countries.[62] A recent study from Japan, where historically HL has been rare before the age of 50 years, reported increasing incidence of HL in recent decades.[63] For HL, the number of cases between 1998 and 2002 is small (n = 122), making interpretation of the time trend difficult. However, there is evidence of an upward trend of the malignancy over the past decade.[19]

In a recent study on incidence trends for HL among immigrant of Chinese descent in British Columbia in Canada, Au et al found the incidence of HL among Chinese immigrants to be significantly lower than expected from the British Columbia background population (standardized incidence ratio = 0.34; $P < 0.0001$).[18] However, at the same time the incidence was significantly higher than that expected by extrapolating from the Hong Kong Chinese population (standardized incidence ratio = 2.81; $P < 0.0001$).[18] Interestingly, the difference was mainly accounted for by young immigrants diagnosed with nodular sclerosis HL subtype. Although that study was restricted in terms of size, it supports the hypothesis of a combined contribution of genetic, lifestyle, and environmental factors in the pathogenesis of HL. Importantly, the results indicate that extrinsic 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 healthcare planners who are responsible for future allocation of health care resources in these regions.

Late Effects

As discussed earlier, developments in modern therapy have dramatically improved survival significantly for HL patients the past decades. The improved outcomes have been accompanied by long-term toxicity, such as elevated risks of second primary malignancies,[64,65] cardiovascular disease,[66] and infections.[66,67] Second malignant neoplasms now comprise the leading cause of death among long-term survivors of HL,[68] with breast cancer being the most common solid tumor among women.[69] Risk of breast cancer is greatest among women diagnosed with HL at age 30 years or younger[69–71] and is strongly associated with chest radiotherapy for HL. Risk increases up to 8-fold with increasing given radiation dose.[69,71,72] Other reported second cancers include acute nonlymphocytic leukemia, non-HL, lung cancer, stomach cancer, and melanoma.[73] Very similar to the pattern of elevated risk for breast cancer, risks for other second cancer sites are highest among patients treated for HL at younger ages. Also, most solid tumors have been found to start within or at the edge of the irradiated field. Importantly, elevated radiation-related risks for second tumors have been found to increase even 20 to 30 years after therapy.[73] Finally, several studies have reported increased mortality of cardiac disease after mediastinal radiotherapy for HL.[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]

ETIOLOGICAL FACTORS

EBV and Other Candidate Viruses

The EBV has been the major candidate for an infectious etiologic agent causing HL. There is evidence that individuals with a personal history of infectious mononucleosis are at elevated risk of developing HL; that risk is greater among persons infected at older ages and weaker with time since infection.[75] Hypothetically, the observed association with infectious mononucleosis could be due to as yet unidentified factors associated with higher socio-economic status resulting in relatively late infections with EBV. However, based on Scandinavian data, there is no elevated risk of HL among first-degree relatives of cases with infectious mononucleosis, strengthening the case for increased risk with infectious mononucleosis itself.[75]

Previous studies investigating serum have reported altered EBV antibody patterns in HL patients[76,77] including higher mean antibody titers to EBV viral capsid antigen than control subjects, consistent with prior infection. Also, there is serological evidence of elevated antibodies to early antigen and Epstein-Barr nuclear antigen among individuals subsequently diagnosed with HL.[78]

Evidence of EBV genome has been reported in malignant cells of about one third to half of the HL cases.[78] Almost all studies have demonstrated that EBV is more likely to be associated with the mixed cellularity subtype than with the nodular sclerosis subtype.[79] The association of EBV with HL is strongest in children, the elderly, men, and those living in disadvantaged social conditions. The frequency of an EBV association is higher in Asian and Central/Middle American countries than in the United States and Europe.[80,81] 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. All this evidence plausibly argues for the role of EBV in the pathogenesis of HL. However, the EBV genome has only been found within the tumor in about 20% to 40% of HL cases with a prior diagnosis of infectious mononucleosis[82,83] and in around 30% to 40% of young adult cases.[79] The association between infectious mononucleosis and HL has been found to be strongest for EBV-positive (vs. EBV-negative) tumors.[79,82] It has also been hypothesized that EBV is etiologic in cases without viral genomic material within the tumor via a hit-and-run mechanism. However, recent studies have not found evidence to support that hypothesis.[84]

A number of 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 HL. However, there is no consistent evidence indicating that these viruses are important in the etiology of HL.[85] The risk of HL has been found to be elevated among persons infected with human immunodeficiency virus (HIV).[86] Furthermore, it has been observed that HIV-associated HL cases 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.[87] In a recent study investigating lymphoma trends in relation to highly active antiretroviral therapy, it was found that the dramatic decrease of non-HL has been paralleled by an increase of HL.[8] Currently, the underlying mechanisms for that observation remain unknown.

Autoimmunity and HL

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.[88] Previous studies have shown that there is an increased risk of mainly non-HL subsequent to autoimmune conditions including rheumatoid arthritis, Sjögren syndrome, and systemic lupus erythematosus.[89–100] Recent studies focusing on underlying pathophysiologic mechanisms related to lymphomagenesis have provided new evidence establishing differences in the risk of NHL development associated with various autoimmune disorders.[101] Recently, a wide range of autoimmune conditions was evaluated for subsequent risk of HL.[11] Elevated risk of HL 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 of HL was associated with family histories of sarcoidosis and ulcerative colitis. The association between both personal and family history of sarcoidosis and a statistically significant increased risk of HL suggests a degree of shared susceptibility for these conditions.

Transplant and HL

Allogeneic bone marrow transplantation is associated with an elevated risk of developing posttransplant lymphoproliferative disorders (PTLD). Although HL after transplantation is rare, an elevated risk has been reported.[10] Five of 6 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). Rowlings et al[10] pointed out that the long latency of HL after transplant and lack of association with risk factors for posttransplant lymphoproliferative disorders are remarkable and should be explored further for possible insights into pathogenesis.

Previous studies of solid organ transplant patients have not generally found a raised risk of HL. The Israel Penn Transplant Tumor Registry lists HL as the lymphoid malignancy in 2.5% (31 cases) among 1252 diseases after solid organ transplant.[102] EBV nuclear material has been demonstrated in some of the cases of HL after transplantation.[103,104]

Genetic Factors

The importance of genetic factors in HL is indicated by reports of multiply-affected families from case series, a twin study, a case-control study, and population-based registry studies carried out in Utah, Denmark, Israel, and Sweden.[12–17] Our group recently analyzed data from registries in Scandinavia and found significant familial aggregation of HL (RR = 3.1) and other lymphoproliferative tumors.[13] Relative risks were higher in men compared with women, and in siblings of cases compared with parents and offspring. Relatives of earlier onset cases were at higher risk for HL 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 towards defining the pathways leading to development of HL and understanding its complex etiology. Until recently, there have been no comprehensive searches of the genome for HL genes, largely due to the difficulty in assembling informative samples. In 2005, we conducted a genome-wide linkage study in 44 informative high risk HL families. No significant linkages were identified but several regions of the genome including on chromosomes 4, 2, and 11 were strongly suggestive.[105] The findings from this investigation are consistent with recessive inheritance. We recently conducted a candidate gene

association study including unrelated familial HL patients and found associations with the genes IL6, IL4R, IL1R, and LMO_2 (unpublished data). Other studies have also implicated polymorphisms in IL6 as being important in HL etiology.[106–108] Importantly, these results are early steps in the discovery of germ line susceptibility genes and delineation of the pathways involved in development of HL. Future work is needed to better define pathways and to determine their interactions with environmental factors.

Other Factors

On the basis of the shape of the incidence curve for HL by age and gender, Glaser[109] proposed in the mid-1990s that that childbearing potentially could be protective against HL in adult women. Results from Norwegian studies have supported this hypothesis[110,111] but the difference in the shape of the incidence curves between the sexes was not seen in England and Wales.[112]

Prior studies examining occupational exposures and subsequent cancer risk have reported on HL risk. The results on HL risk in relation to exposure to wood, wood dust and chemicals are generally inconsistent and based on small numbers. Phenoxy herbicides and chlorophenols have also been investigated but, again, consistent evidence of a causal association is lacking.[113] There is no evidence of an association of ionizing radiation with risk of HL. Some studies have found elevated risk of HLs after tonsillectomy, however, the results are inconsistent. Many studies of clustering have been reported, however, a review by Mueller and Grufferman concludes "there is no persuasive evidence of meaningful time-space clustering of HL." In general, studies of environmental, chemical, and occupational risk factors in HL generally reveal only weak and inconsistent evidence.[114]

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