Non-Hodgkin's Lymphoma

Lymphomas are cancers involving the cells of the lymphatic system. The majority of lymphomas involve the lymph nodes and spleen but the disease may also affect other areas within the body. Non-Hodgkin's lymphoma (NHL) is a classification of all lymphomas except Hodgkin's disease. Thus NHL is a mixed group of diseases that is characterized by the malignant increase in specific cells of the immune system (B or T lymphocytes). B-cell lymphomas are more common than T-cell lymphomas, accounting for about 85% of all cases of NHL (ACS, 2003). The various types of NHL are thought to represent different diseases with different causes (Scherr and Mueller, 1996). NHL can occur at all ages, however, the average age at diagnosis is in the early 60s and the incidence of this disease generally increases with age. This disease is more common in men than in women and affects whites more often than African Americans or Asian Americans (ACS, 2003). The American Cancer Society estimates that approximately 56,390 Americans will be diagnosed with NHL in 2005, making it the fifth most common cancer in the U.S. among women and the sixth most common cancer among men, excluding non-melanoma skin cancers (ACS, 2005).

Overall, between 1973 and 1997, the incidence of NHL in the U.S. grew 81% (Garber, 2001), although during the 1990s, the rate of increase appears to have stabilized (ACS, 2005). In Massachusetts, the incidence of NHL increased 50% during 1982-1997 from 10.5 cases per 100,000 to 15.7 cases per 100,000 (MCR, 1997 and 2000). The increase in NHL incidence has been attributed to better diagnosis, greater exposure to causative agents, and, to a lesser extent, the increasing incidence of AIDS-related lymphomas (Devesa and Fears, 1992; Scherr and Mueller, 1996). Although the primary factors related to the development of NHL include conditions that suppress the immune system, viral infections, and certain occupational exposures, these factors are thought to account for only a portion of the increase observed in this cancer type (Scherr and Mueller, 1996). The observation that the rate of increase is declining for NHL may be attributed in part to increased use of antiretroviral therapy to slow HIV progression (Wingo et al., 1998).

NHL is more common among people who have abnormal or compromised immune systems, such as those with inherited diseases that suppress the immune system, individuals with autoimmune disorders, and people taking immunosuppressant drugs following organ transplants. Genetic predisposition (e.g., inherited immune deficiencies) only accounts for a small proportion of NHL cases (Scherr and Mueller, 1996). AIDS patients have a 100- to 300-fold higher risk for NHL than the general population (again, these cases account for only a minor part of overall NHL incidence) (Garber, 2001). NHL has also been reported to occur more frequently among individuals with conditions that require medical treatment resulting in suppression of the immune system, such as cancer chemotherapy. However, current evidence suggests that the development of NHL is related to suppression of the individual's immune system as a result of treatment, rather than the treatment itself (Scherr and Mueller, 1996).

Several viruses have been shown to play a role in the development of NHL. Among organ transplant recipients, suppression of the immune system required for acceptance of the transplant leads to a loss of control or the reactivation of viruses that have been dormant in the body (e.g., Epstein-Barr Virus [EBV] and herpesvirus infections). In addition, because cancer-causing viruses are known to cause lymphomas in various animals, it has been proposed that these types of viruses may also be associated with the development of NHL among humans without compromised immune systems. Infection with the human T-cell leukemia/lymphoma virus (HTLV-I) is known to cause T-cell lymphoma among adults. However, this is a relatively rare infection and most likely contributes only a small amount to the total incidence of NHL (Scherr and Mueller, 1996). EBV infection is common among the general population

and has been shown to play a role in the development of most cases of transplant and AIDS related NHL. The combination of immune system deficiencies and EBV infection may cause some people to develop NHL (ACS, 2003). Although viruses are causal factors for some subtypes of NHL, to date, studies have shown that the role of EBV in the development of NHL in the general population may not be large (Scherr and Mueller, 1996). Moreover, the high prevalence of EBV in the general population suggests that EBV may be only one of several factors in the development of this cancer.

Recent studies have found that a type of bacteria, *Helicobacter pylori*, a common cause of stomach ulcers, can also cause some lymphomas of the stomach (ACS, 2003). An important implication of this finding is that treatment with antibiotics could prevent some NHL of the stomach.

Some occupations have been associated with an increased risk of developing NHL, such as occupations related to chemicals or agriculture. Farmers, herbicide and pesticide applicators, and grain workers appear to have the most increased risk (Zahm, 1990 and 1993; Tatham et al., 1997). Studies conducted among agricultural workers have demonstrated increases in NHL among those using herbicides for more than 20 days per year and individuals who mix or apply herbicides. A greater incidence of NHL appears to be related specifically to exposure to the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) and organophosphate insecticides (Wigle et al., 1990; Zahm et al., 1990; Zahm et al., 1993). Further studies of exposure to these chemicals and NHL incidence have shown that the increased risk is attributed to a specific impurity, 2,3,7,8-tetrachlorodibenzo-p-dioxin or 2,3,7,8-TCDD, present in these herbicides. However, reports of accidental industrial exposures to TCDD alone have not demonstrated an increased risk of NHL (Scherr and Mueller, 1996). An elevated risk for NHL development has also been noted among fence workers, orchard workers, and meat workers. High-dose exposure to benzene has been associated with NHL (ACS, 2003), however, a recent international cohort study indicated that petroleum workers exposed to benzene were not at an increased risk of NHL (Wong and Raabe, 2000).

In addition, epidemiological studies of long-term users of permanent hair coloring products have suggested an increased incidence of NHL (Zahm et al., 1992; Scherr and Mueller, 1996). However, a recent population based study found no association between the use of hair color products and an increased risk of developing NHL. The researchers further stated that results from this study and previous studies, including experimental animal studies, provide little convincing evidence linking NHL with normal use of hair dye (Holly et al., 1998).

Although radiation (e.g., nuclear explosions or radioactive fallout from reactor accidents) has been implicated in the development of some cancers, including NHL (ACS, 2003), there is little evidence for an increased risk of lymphoma due to radiation (Scherr and Mueller, 1996).

Recent studies have suggested that contamination of drinking water with nitrate may be associated with an increased risk of NHL (Ward et al., 1996). Nitrate forms N-nitroso compounds which are known carcinogens and can be found in smoked or salt-dried fish, bacon, sausages, other cured meats, beer, pickled vegetables, and mushrooms.

Smoking has also been suggested to increase the risk of NHL. A study that evaluated the history of tobacco use and deaths from NHL determined that people who had ever smoked had a two-fold increase of dying from NHL as compared to those who never smoked. Further, a four-fold increase was found among the heaviest smokers (Linet et al., 1992). In addition, a more recent study that primarily examined occupation and NHL risk found a significant association with high levels of cigarette smoking and all NHL types (Tatham et al., 1997). However, a recent review of 5 cohort studies and 14 case-control studies concludes that results of epidemiological studies have been inconsistent and that smoking

has not been determined to be a definitive risk factor in the development of NHL (Peach and Barnett, 2000).

A recent Danish study has linked the use of tricyclic and tetracyclic antidepressants to NHL, however, more research is needed on this possible association (Dalton et al., 2000).

Although NHL is associated with a number of risk factors, the causes of this disease remain unknown. Most patients with NHL do not have any known risk factors (ACS, 2003).

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