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Cancer Res 1992;52:5496s-5500s. Published online October 1, 1992.

[CANCER RESEARCH (SUPPL.) 52, 5496s–5500s, October 1, 1992]

Increasing Incidence of Non-Hodgkin's Lymphoma: Occupational and Environmental Factors[1]

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Abstract

The incidence of non-Hodgkin's lymphoma (NHL) has been increasing steadily for the last 30 years, and attention is being focused on the possible causes of this increase. Possible explanations have included the exposure to viruses, radiation, nutrition, and pesticides, and these issues are addressed by other presentations in this workshop. The interest in a possible role of pesticides stems from the observation that farmers have an increased risk of NHL. However, farmers may also be exposed to oncogenic viruses carried by farm animals, and studies of abattoir workers and meat inspectors have found increased risks of NHL; although these findings are unlikely to be directly relevant to the general population, they do complement other suggestions that exposure to oncogenic viruses may be a factor in the general increase in NHL. Farmers may also be exposed to chronic antigenic stimulation which may increase the risk of NHL. This latter observation is consistent with the observation that NHL is associated with several autoimmune diseases which involve chronic antigenic stimulation. NHL has also been associated with a number of occupational exposures but these are generally rare and the findings are inconsistent, although a number of studies have found an increased risk of NHL in work involving exposure to wood, solvents, or related chemicals. Perhaps the strongest evidence of an association with an environmental exposure comes from two studies showing that use of hair dyes increases the risk of NHL. This exposure is relatively common in women, and hair dye use may account for approximately 20% of all NHL cases in women. However, it is not known if hair dye use has increased during the last 40 years. The evidence for an increased risk of NHL from other life-style factors such as alcohol, tobacco, and medication is generally weak and inconsistent.

Introduction

The incidence of NHL[3] has been increasing steadily for the last 30 years in several countries and has increased by more than 50% in the last 16 years in the United States (1). Some of this increase is due to lymphomas in patients with acquired immunodeficiency syndrome, but this does not appear to account for the majority of the increase. Attention is therefore increasingly being focused on the possible causes of this dramatic increase. Possible explanations have centered on the likely roles of viruses, pesticides, radiation, and nutrition, and these issues are addressed by other presentations at this workshop. In this article I will discuss other possible occupational and environmental causes of the increase in NHL.

This paper is not intended to be a review of all known or possible risk factors for NHL. Rather, I will address only exposures which are sufficiently common that they could have contributed to the increase in NHL or which are of scientific relevance to other factors which could have contributed.

In recent years, particular attention has been focused on the increased risks of NHL in farmers and other agricultural workers. Although most studies of this issue have focused on exposures to pesticides (which are discussed elsewhere in this issue), several other agricultural exposures have also merited investigation. This article has, accordingly, been divided into three sections: (*a*) possible roles of these other agricultural exposures; (*b*) other occupational exposures; (*c*) other environmental exposures such as hair dyes, alcohol, and cigarette smoking.

Agricultural Exposures

Agricultural work involves a wide variety of tasks, each involving potentially carcinogenic exposures. Farmers and farm laborers may come into contact with animal viruses, bacteria and fungi, pesticides, solvents, fuels and oils, and dusts (2). Other agricultural workers such as fencing workers, abattoir workers, meat inspectors, and veterinarians experience some of the same exposures. Agricultural workers have been consistently found to have elevated risks for non-Hodgkin's lymphoma and other hematological malignancies. The increase in mortality in the United States from NHL and other hematological cancers during 1950–1980 has primarily occurred in farming states (3). Similar patterns have been observed in New Zealand (4), but there has been little increase in NHL incidence in Sweden (5).

The factors responsible for the increased risks of NHL in farmers are not well understood, but most studies have focused on pesticides. However, farmers are also exposed to other agricultural chemicals, zoonotic viruses, and factors which increase chronic antigenic stimulation and these other aspects of farming will be considered here (6).

Other Agricultural Chemicals. As noted above, most epidemiological studies have focused on pesticides (insecticides or herbicides), but farmers are exposed to other chemicals including solvents, emulsifiers, fuels, and oils. Agricultural chemicals may also be used in other situations, such as for wood treatment and preservation, and a New Zealand study found a small excess risk of non-Hodgkin's lymphoma in fencing workers (7, 8) (the more general category of wood workers is discussed below). However, virtually all studies of agricultural chemical exposures have concentrated on pesticides, and very little information is available on cancer risks of nonpesticide chemical exposures in agriculture. Nevertheless, some descriptive studies involving census tract data, which have noted associations between NHL and sales of pesticides, have also found associations with sales of fuel, oil, and other farm chemicals and these latter associations may warrant further investigation (9).

Zoonotic Viruses. Although epidemiological evidence for the role of oncogenic animal viruses in human cancer is currently weak (2), a number of potentially oncogenic zoonotic viruses exist in the agricultural environment. These include the herpes virus which causes Marek's disease in poultry (10) the avian leukosis virus (11), papilloma viruses in cattle (12, 13), and perhaps other currently undetected viruses. The rapid proliferation of information concerning retroviruses suggests that other members of this family will be found in domestic animals as well as humans. Thus, although exposure to farm animal

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[1] Presented at the National Cancer Institute Workshop, "The Emerging Epidemic of Non-Hodgkin's Lymphoma: Current Knowledge Regarding Etiological Factors," October 22–23, 1991, Bethesda, MD. This work was conducted during the tenure of a Senior Research Fellowship from the Health Research Council of New Zealand.

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[3] The abbreviations used are: NHL, non-Hodgkin's lymphoma; BLV, bovine leukemia virus; RR, relative risk; CI, confidence interval; PMR, proportionate mortality risk.

viruses could not directly account for the increase in NHL in the general population, it is of relevance to the more general issue of the causation of NHL by viruses in the general population.

Most interest has centered on BLV, an exogenous C-type retrovirus which has been established as the etiological agent of the adult form of bovine lymphosarcoma (14). The virus is related closely to human T-cell leukemia virus 1, the cause of adult T-cell leukemia in humans (15). BLV has been found in herds in most countries, including the United States and New Zealand (16), and has also been found in meat and unpasteurized milk (17). Although BLV is killed by pasteurization, consumption of unpasteurized milk is extremely common among farm families and rural residents (18). BLV can also infect sheep and goats and can cause cancer in sheep (15), and it is capable of infecting human cells and inducing syncytia in tissue culture (19). However, human studies, including studies of NHL cases in children, have not shown evidence of infection (20), and it is becoming increasingly unlikely that this virus increases the risk of NHL in humans. Nevertheless, there are other oncogenic viruses carried by farm animals, including papilloma viruses, which have apparently not been adequately studied to date, and the possibility remains that some of these other viruses play a role in human cancer.

Possible leads have been suggested by recent studies of abattoir workers, a group which may have high exposure to animal viruses (21). In particular, two New Zealand case-control studies have found increased risks of NHL in abattoir workers (7, 8), and a cohort study (22) of mortality in 13,844 white male members of a meatcutters' union in Baltimore, MD, found elevated risks for Hodgkin's disease (ICD 201) and for cancer of other lymphatic tissue [which included NHL cases registered under ICD 202 and multiple myeloma (ICD 203)]. No increased risk was observed for NHL cases registered under ICD 200.

Abattoir work may involve significant chemical exposures in the pelt department and in meat wrapping, but the New Zealand studies did not involve meat wrappers and found that pelt department workers had risks similar to those of other abattoir workers (21). Johnson *et al.* (22) have also noted that the greatest risk for Hodgkin's disease in their study of male abattoir workers was associated with slaughtering, particularly of cattle, pigs, and sheep. This finding is consistent with the suggestion of a viral etiology, and this is currently the leading hypothesis to explain the findings for abattoir workers (21).

Veterinarians are another occupational group with exposure to farm animals. There is inconsistent evidence that veterinarians may be at increased risk for hematological malignancies. Blair and Hayes (23) studied 5016 deaths in white male veterinarians and found elevated risks for Hodgkin's disease (PMR = 1.87; 95% confidence interval, 1.11–2.96) and cancer of other lymphatic tissue (PMR = 1.92; 95% confidence interval, 1.26–2.82). Interestingly, the PMR for all hematological malignancies was elevated in meat inspectors (PMR = 3.36; 95% confidence interval, 1.44–6.57), a finding consistent with the increased risks in abattoir workers.

These increased risks of NHL in abattoir workers and meat inspectors are most likely to be due to exposures to zoonotic viruses or chronic antigenic stimulation (see below). Certainly, they are unlikely to be due to chemical exposures, since these are trivial in most abattoirs. Thus, further studies of meat workers would be valuable in clarifying whether exposures to zoonotic viruses contribute to the excess risk of NHL in agricultural workers. Farm animal viruses are very unlikely to be a major factor in the increase in NHL in the general community because the prevalence of exposure is low. However, the possibility of an excess risk of NHL from exposure to farm animal retroviruses does complement suggestions that other retroviruses (in addition to human immunodeficiency virus) carried by humans could be playing a role in the more general increase in NHL in the community.

Chronic Antigenic Stimulation. A third group of possible etiological factors is suggested by the hypothesis that NHL is a complication of the autoimmune process and may occur after prolonged antigenic stimulation (24, 25). For example, Cunningham (26) has suggested that ingestion of animal proteins, particularly bovine protein, results in chronic stimulation of lymphoid tissue which might act in combination with other factors such as oncogenic viruses to induce malignant change. There are other sources of chronic antigenic stimulation which may also be more prevalent in agricultural communities. For example, some farmers might have continual exposure to grain, and abattoir workers, who have increased risks of NHL (see above), might have continual exposure to animal protein. A proportionate mortality study of workers in the grain industry (27) found elevated risks for NHL, although the excess was concentrated in flour mills where pesticides are used more frequently than in other parts of the industry.

More generally, several autoimmune diseases which are characterized by persistent antigenic stimulation have been associated with NHL, including rheumatoid arthritis, systemic lupus erythematosus, and celiac disease (8, 24, 28). There is a high incidence of NHL in renal transplant patients (25), but most of these are in the brain which is an uncommon site of involvement. More generally, patients who have received immunosuppressive therapy appear to have an increased risk of NHL, and the increasing use of this therapy will have contributed to the rise in NHL, although the numbers involved are likely to be very small (29).

NHL may also be associated allergic diseases such as eczema, asthma, hay fever, and general allergies (8). Although the epidemiological evidence linking these diseases to NHL is weak and inconsistent, these hypotheses are of particular interest in light of recent evidence that allergic disease is on the increase. For example, although there is still considerable debate about recent trends (30), there is now reasonably consistent evidence of increases in asthma prevalence in several countries (31–34). It is currently unclear whether this is due to an increase in allergens, or whether modern asthma management, by providing symptomatic relief, has encouraged continuing exposure to allergens in susceptible persons. Whatever the explanation, the apparent increase in allergic diseases could be relevant to the continuing increase in NHL.

Other Occupational Exposures

A number of different occupations have occasionally been reported to be associated with NHL (24, 25), including sales and clerical work, engineers, mechanics, machinists, metal workers, chemists, vinyl chloride workers, rubber workers, anesthesiologists, workers in the food industry, leather workers, and road transport workers. However, most of these associations have not been very strong or consistent and have involved rare occupations. Thus, they are very unlikely to be account for a significant proportion of the general increase in NHL. Similarly, although a number of paternal occupational exposures have been associated with childhood cancer (35, 36), these are

also inconsistent and involve rare occupations and are therefore unlikely to be of major importance to the causation of NHL in children.

I will briefly discuss several occupational associations which are of interest, either because they involve relatively common exposures or because they are relevant to more widespread environmental exposures.

Wood. Wood and wood products are among the most common occupational exposures, and several studies have reported excesses of hematological cancers in wood workers (37). It is currently unclear whether the excess risks are due to the wood dust itself, the various chemicals that are applied to the wood, or other carcinogenic agents involved in working with wood. It is of interest that the related occupations of forestry work (38) and pulp and paper work (39) have also been found to carry an increased risk of lymphomas, although these findings have been inconsistent. These occupations involve exposure to herbicides or chlorophenols, but sawmill workers may also have exposure to chlorophenols and there is inconsistent evidence of an increased risk of NHL (7, 8, 40). Overall, although these various occupations are not uncommon, their associations with NHL are relatively weak and inconsistent and are unlikely to be of importance to the general increase in NHL.

Solvents and Other Chemicals. Solvents have been associated with NHL in a number of studies (41–43), including studies of rubber workers (44), aircraft maintenance workers (45), and dry cleaners (46). In particular, benzene exposure increases the risk of NHL, and it has been suggested that this may be due to its effects on the immune system (42), but it also appears that the number of clonal chromosome aberrations is especially large in NHL patients with a history of occupational exposure to organic solvents (47). Clusters of NHL cases have been observed in a community living near industrial plants (48), including a chemical recycling plant which has released solvent vapors (49). Other occupations which might involve exposure to solvents or related chemicals and which have been reported as being at increased risk of NHL include those of highway workers (50), petroleum refinery employees (51–53), styrene workers (54), chemists (55, 56), and chemical manufacturers (57, 58).

Finally, some studies have found a correlation between NHL mortality and levels of trihalomethanes in drinking water (59). Although relatively little is known about the relationship between drinking water contaminants and NHL, the ubiquitous nature of the exposure means that further research would be justified.

Electromagnetic Fields. In recent years there has been considerable controversy regarding the hypothesis that exposure to electromagnetic fields may increase the risk of cancer (60). This concern has arisen from studies which have reported excess risks of adult cancer from occupational exposures and excess risks of childhood cancer from residential exposures. Although there have been occasional reports of excess risks of NHL in some electrical occupations (24, 61, 62) these findings are not consistent and the occupational data primarily show small increased risks of leukemia and brain tumors rather than NHL (63). Some residential studies have also shown small increased risks of NHL in adults residing near electricity transmission facilities (64–66), but once again the findings are weak and inconsistent. It therefore appears unlikely that occupational or environmental exposures to electromagnetic fields are a major cause of NHL in adults, although the possibility exists that there may be a weak effect from occupational and residential exposures. On the other hand, the ubiquitous nature of the exposure means that even a small risk could result in significant effects; further research is therefore warranted, and a number of major studies are currently in progress.

There has also been considerable controversy concerning the possibility that residential exposures to electromagnetic fields can increase the risk of childhood cancer. The debate on this issue is likely to continue for a number of years (67), particularly since the findings to date have been more strongly related to wiring configurations than measured fields (60, 68, 69). However, the evidence is certainly becoming more consistent over time, and there are no obvious strong confounding factors which have not been taken into account. Although NHL accounts for only about 5% of childhood cancer (70), the two major studies to date (68, 69) have both found relative risks of childhood lymphomas associated with electromagnetic field exposure which were similar to, or greater than, the relative risks for childhood cancer in general. Savitz (69) estimated that, if the association is causal, electromagnetic field exposure could account for 10–15% of childhood cancers; similar estimates would apply to childhood cases of NHL.

Other Exposures

Hair Dyes. The environmental exposure which seems most likely to have contributed to the increase in NHL is that of hair dyes. These contain substances that are mutagenic and carcinogenic in animals, and several studies have reported excess risks of hematological cancers in cosmetologists and hairdressers (71).[4] Two case-control studies have examined risks of NHL in users of hair dyes.

The first such study (71) was limited to men and found that risk increased with frequency and duration of hair dye use. The overall relative risk associated with hair dye use was 2.0 (95% CI, 1.3–3.0), but only 3% of controls reported using hair dyes and the population attributable risk was only 3%.

A more recent study[4] also examined risks in women. Use of any hair-coloring product carried a relative risk of 1.5 (95% CI, 1.1–2.2) for NHL, and the risk was slightly higher among users of permanent hair-coloring products (RR = 1.7) than for users of semi- or nonpermanent hair-coloring products (RR = 1.4). The risk appeared to be greater among those women using dark hair-coloring products. Long duration and early age of first use were also associated with a particularly increased risk, but there were no consistent patterns for frequency of use. The authors noted that these findings are somewhat consistent with what would be expected based on the concentration and formulation of the various hair-coloring products.[4] Although it is possible that the findings could be due to recall bias, it seems unlikely that this would selectively operate for particular types of hair dyes,[4] and there was little evidence of recall bias in a similar study of breast cancer patients (72). It also seems unlikely that the findings are due to confounding, although this can never be ruled out, and the possibility remains that the findings are due to chance.

Overall, 46% of the women in the control group had used hair-coloring products, and the authors commented that if the association is causal the use of hair-coloring products would account for 20% of all NHL cases in women. In contrast, only 7% of the men in the control group had used hair-coloring

[4] S. H. Zahm, D. D. Weisenburger, P. A. Babbitt, *et al.* Use of hair coloring products and the risk of lymphoma, multiple myeloma, and chronic lymphocytic leukemia, unpublished observations.

products, and the relative risk estimate in men was not elevated (RR, 0.8; 95% CI, 0.4–1.6).

When considered together, these two studies indicate that use of hair dyes could be a major cause of NHL in women and would account for a greater percentage of NHL cases than any other known risk factor. However, data are not available in time trends in hair dye use, so it is not possible to estimate the extent to which increases to hair dye use may have contributed to increases in NHL incidence.[4] The current population attributable risk of 20% gives some idea of the maximum contribution of hair dyes to the increase in NHL, although this is likely to be an underestimate due to misclassification of exposure (73) (by contrast, the increase of 50–60% in the last 16 years means that approximately 35% of current NHL cases are "excess" cases which are related to the recent increase in incidence). Hair dyes are unlikely to be a major cause of NHL in men because the prevalence of exposure is low.

Other Lifestyle Factors. NHL is slightly more common in urban areas, in whites, and in the upper socioeconomic groups (74), but the reasons for these patterns are unknown, and they are unlikely to be relevant to the continuing increase in NHL. One study has found a (non-significant) association between tobacco use and lymphomas (75), but there was no evidence of a dose-response relationship, and most other studies of tobacco and NHL have found no association. Similarly, most studies have found no association between NHL and alcohol consumption (75). Finally, several studies have found that particular medications might increase the risk of developing NHL (24), but the evidence is relatively weak with the exception of immunosuppressive therapy (discussed above), and the exposures are rare.

Summary

In summary, the incidence of NHL has been increasing steadily for the last 30 years, and attention is being focused on the possible causes of this increase. Possible explanations have included the exposure to viruses, radiation, nutrition, and pesticides, and these issues are addressed by other presentations in this workshop. The interest in a possible role of pesticides stems from the observation that farmers have an increased risk of NHL. However, farmers also have exposure to oncogenic viruses carried by farm animals, and studies of abattoir workers and meat inspectors have found increased risks of NHL. Farmers might also be exposed to chronic antigenic stimulation which could increase the risk of NHL. This latter observation is consistent with the observation that NHL is associated with several autoimmune diseases which involve chronic antigenic stimulation. NHL has also been associated with a number of occupational exposures but these are generally rare and the findings are inconsistent, although a number of studies have found an increased risk of NHL in work involving wood or exposure to solvents or related chemicals.

Perhaps the strongest evidence of an association with an environmental exposure comes from two studies showing that use of hair dyes increases the risk of NHL. This exposure is relatively common in women, and hair dye use may account for approximately 20% of all NHL cases in women. However, it is not known if hair dye use has increased during the last 40 years. The evidence for an increased risk of NHL from other life-style factors such as alcohol, tobacco, and medication is generally weak and inconsistent. Thus, the single factor which is most likely to account for a significant proportion of the increase in NHL is hair dye use, but this consideration predominantly applies to women and it is unlikely to explain the increase in incidence in men. On the other hand, some occupational exposures to solvents and related chemicals could explain the increase in incidence in men but could be less relevant to NHL in women.

More generally, there is increasing evidence that NHL can be caused by retroviruses, including the human immunodeficiency virus, and it is possible that exposure to such viruses is increasing. In this context, it is of interest that NHL appears to be a complication of the autoimmune process and might occur after prolonged antigenic stimulation. It is therefore possible that the increase in NHL is also partly related to an increase in exposure to factors which increase antigenic stimulation, but there is very little epidemiological evidence to assess this speculation.

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