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Quantification of the Impact of Known Risk Factors on Time Trends in Non-Hodgkin's Lymphoma Incidence[1]

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Abstract

The incidence of non-Hodgkin's lymphoma among white men in the United States was measured as 6.9/100,000 person-years in 1947–1950 and as 17.4 in 1984–1988. We have estimated how much the known and suspected diagnostic and risk factors might have contributed to this apparent increase of 152%. Firm conclusions cannot be drawn without more data on risk and changes in prevalence, but a reasonable range of impacts can be constructed. After accounting for the likely effects of misdiagnosis of Hodgkin's disease as non-Hodgkin's lymphoma, of the acceptance of new entities of non-Hodgkin's lymphoma, of familial factors, of human immunodeficiency virus and other immunosuppressive conditions or drugs, and of occupation, we estimate that the percentage increase in incidence was still 80% among all males and 42% among those aged 0–64. An agent carrying a relative risk of 2.0 rising in prevalence from 0 to 42% would account for the latter rise. Diet, hair dyes, and general environmental exposures to pesticides may be contributing, but currently estimated risks and changes in exposure levels do not appear large enough to account for the residual rise. Among men aged 75–84, some of the residual rise of 109% probably is diagnostic, but only further research will clarify the issue.

Incidence

The measured incidence of NHL[3] in the United States grew enormously from the late 1940s to the late 1980s (1). The incidence rose elsewhere in the world as dramatically as in the United States. Mortality rates rose, too. Men and women, whites, and other races all showed striking increases.

The rates presented here are all either standardized for age or specific for age, so the aging of the population *per se* accounts for none of the increase. Over the past 2 decades, the high percentage of incident cases confirmed by pathology and the low percentage of cases reported only at death suggest that the registration is rather complete, so explanation of the increase must be sought elsewhere.

The pattern of age- and time-specific rates does not suggest a clear-cut cohort effect such as is seen for lung cancer. On the other hand, as the analysis of Holford *et al.* (2) showed, some cohort effect appears in the older age groups. Diagnostic practices have shifted, and exposures to some of the putative causes of NHL have increased. We have estimated what the impact of various factors might be on NHL incidence, acknowledging the potential for large error.

We used published (1) and unpublished data from 4 geographic areas of the United States that had cancer registry data spanning the 40-year period (Atlanta, GA; Detroit, MI; San Francisco, CA; and Connecticut).

The incidence of NHL rose 3.1% per annum among white men and 2.9% per annum among white women. All age groups showed marked increases, but the rate of increase varied. The family of age-specific trend lines shows a splayed pattern, as presented by Devesa and Fears (3). Elderly white men evidenced the greatest change in incidence. The rate grew from 19/100,000 person-years to 99 among white men aged 75–84 (Table 1). Young white women showed the least: from 1.6 to 2.3. Because medical care and diagnosis might be more consistently complete for men in the labor force, we also present the rate among men younger than 65.

We will use the increase of 10.5 cases/100,000 person-years in the age-adjusted white male rate (6.9 in 1947–1950 to 17.4 in 1984–1988) as a starting point for calculation. It is reasonable to attempt to explain the incidence rise over the entire 40-year period because some of the exposures that might explain the increase were virtually absent 40 years ago, but not 20 years ago. The average annual rate of increase from the late 1940s to the early 1970s was quite similar to the rate from the early 1970s to the late 1980s.

Diagnosis

As seen in Devesa and Fears' (3) presentation, the overall rate of Hodgkin's disease has not declined. Nonetheless, some NHL cases were misdiagnosed as Hodgkin's in the past, and fewer are now, as mentioned in the presentation by Banks (4). Table 2 shows data excerpted from a study of the misclassification of Hodgkin's disease by Glaser and Swartz (5). Seventeen % of the cases originally diagnosed as Hodgkin's disease in 1969–1974 were deemed not to be Hodgkin's after pathology review, and most of the misdiagnosed cases were NHL. This error occurred only 5% of the time among cases originally diagnosed as Hodgkin's disease in 1980–1984. The error rate was similar in men and women but much worse in the elderly than the young.

Misdiagnosis of NHL as Hodgkin's disease probably was even more common before the 1970s. We have assumed that 70% would have been confirmed as Hodgkin's disease in the late 1940s and 30% would not, that 60% of the false-positives were actually NHL, and that the error rate was very high in the elderly and lower in the young. Applying these hypothetical error rates to 1947–1950 incidence rates of Hodgkin's disease (Table 3) reveals that perhaps 0.6 additional white male case/100,000 person-years might be explained by improved diagnostic distinction of Hodgkin's disease from NHL, increasing the NHL rate from 6.9 to 7.5 and reducing the difference from 10.5 to 9.9. The addition of the presumed missed cases of NHL to the measured baseline affects the other 1947–1950 rates very little, but perceptibly narrows the difference in the young women from 0.7 to 0.3. (Anecdotal data suggest that the opposite error, mislabeling of true Hodgkin's disease as NHL, happens quite infrequently.)

Apart from Hodgkin's disease, other disease entities are now included in NHL that formerly were not. The consensus among the pathologists is that these new NHL entities probably account for not more than 5% of NHL.

In addition, there is more thorough diagnosis than there was 40 years ago, especially among older patients. We have no reliable data on the extent of this diagnostic improvement. We

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[3] The abbreviations used are: NHL, non-Hodgkin's lymphoma; HIV, human immunodeficiency virus.

Table 1 *Measured NHL incidence rates among whites in the United States (40 geographic areas)*[a]

	1947–1950	1984–1988	Difference	% change
Males	6.9	17.4	10.5	152
Females	4.7	11.6	6.9	147
Males 75–84	19.2	99.5	80.3	418
Males 0–64	5.1	10.5	5.4	106
Females 25–34	1.6	2.3	0.7	44

[a] Cases per 100,000 person-years, age-adjusted using the 1970 United States standard.

Table 2 *Rate of confirmation of Hodgkin's disease (%)*

Age	1969–1974	1980–1984
25–34	92	95
35–44	84	95
45–54	78	98
55–64	60	92
65–74	51	79
75+	33	83
All ages	83	95

will assume that fully one-half of NHL diagnosed among people over age 74 in the late 1980s would not have been so diagnosed in the 1940s; this would make the rate of increase in the elderly similar to that in the younger. We further assume that 20% of NHL in people aged 65–74 and 8% in people under 65 would not have been properly identified, because the illness was one of the entities newly recognized as NHL, was diagnosed as an unrelated illness, or was not diagnosed at all. These age-specific rates would yield an age-adjusted overall rate adjustment of 10%.

Viruses

HIV infection can produce NHL, either as the AIDS-defining event or as a later effect. The rise in prevalence of HIV infection may have an overwhelming effect on the total NHL burden during the next decade (6), but it had little impact during the period we are considering, except possibly in San Francisco in the most recent few years. The NHL rate among white men grew by 51% in the 4 geographic areas from 1975–1978 to 1985–1988, while it grew 45% in the 3 areas other than San Francisco. If it had grown 45% in the 4 geographic areas, the 1985–1988 rate would have been 0.7 case/100,000 person-years lower than it was. We will assume that the NHL rates in women or elderly men were uninfluenced by HIV in the 1984–1988 period.

As discussed by Mueller *et al.* (7), human T-cell leukemia virus-1 is a very rare virus in the United States and cannot account for the rise in NHL. Epstein-Barr virus infection, the immune response to it, or the age at which it occurs may influence NHL risk (8). Because Epstein-Barr virus is nearly ubiquitous and probably has been for the whole period, the simple prevalence of Epstein-Barr virus infection cannot explain the rise in NHL, so a more subtle mechanism would be required. In theory, some other virus could have contributed to the rise, but no clear candidates are now proposed.

Familial Factors

Filipovich *et al.* (9) described some of the strong genetic effects, for example, the association between ataxia telangiectasia and NHL, but the syndromes linked to NHL are very rare and account for only a tiny portion of the total NHL burden in the population. We can detect a familial association (10, 11) in the general population, with an attributable proportion in Yorkshire or in the midwestern United States of 3–4%, but we do not know whether this effect adds to or multiplies the effects of environmental exposures. If we assume that the gene pool has not changed over this 40-year period, then the familial effect either contributed nothing to the trend or amplified the effects of some environmental changes within a small subgroup of the general population. If we assume an additive effect and wish to restrict our attention only to the part of the incidence that is nonfamilial, we could subtract between 0.3 and 0.45 case/100,000 person-years from the overall rates in both 1948 and 1988. Such a restriction to the nonfamilial cases would not affect the difference in rates over time, but it would increase slightly the percentage rise in rates.

Medical Conditions and Drugs

Several powerful immunosuppressant drugs given to organ transplant recipients dramatically and immediately increase the risk of developing NHL, but these drugs are given to very few people. Cancer chemotherapy agents moderately suppress immune response and moderately increase NHL risk, but these, too, are uncommon exposures. There are common exposures that mildly suppress immune activity, including steroids, but in most analytic studies, these common exposures bear inconsistent and weak relation to NHL risk. On balance, the increased use of these immunosuppressive drugs promises to explain very little of the NHL increase.

Based upon the published data of Cartwright *et al.* (11) and Tielsch *et al.* (12), we can infer that asthma, allergies, arthritis, rheumatic fever, tuberculosis, and mononucleosis have, at most, a modest association with risk. Some of these conditions have shown some increased risk in the data presented by Bernstein and Ross (13) and Scherr *et al.* (14) and in other data. These medical conditions warrant further study. Some, like asthma, may have risen in prevalence in the United States over the last 40 years, but whether prevalence has risen in other areas of the world with rising NHL rates is uncertain.

Radiation

As shown by Boice (15), it is very unlikely that ionizing radiation has affected the population NHL risk. Indeed, it is not clear that such exposures affect rates of NHL at all.

Occupation

People who have worked in occupations with exposures to industrial solvents, vinyl chloride, or herbicides have been shown to have increased risk of NHL: benzene workers, chemists, farmers, grain handlers, petroleum refinery workers, anesthesiologists, pathologists, wood workers, and others (11, 12, 16–18). The portion of NHL that can be attributed to these occupational exposures varies from 4 to 11% in recent studies (Table 4).

Table 3 *Estimated incidence of NHL misdiagnosed as Hodgkin's disease among whites in the United States 1947–1950*

	Assumed true positive rate (*a*)[a]	Hodgkin's disease rate (cases/100,000 person-yrs) (*b*)	Additional NHL (cases/100,000 person-yrs) (*c*)	Adjusted NHL (cases/100,000 person-yrs) (*d*)
Males	0.70	3.2	0.6	7.5
Females	0.70	2.2	0.4	5.1
Males 75–84	0.20	5.2	2.5	21.7
Males 0–64	0.75	2.8	0.4	5.5
Females 25–34	0.80	3.4	0.4	2.0

[a] $c = (1 - a) \times 0.60 \times b$; $d = c$ + Column 1 of Table 1.

Table 4 *Occupational attributable proportions*

Population	Period	Occupational exposure	Relative risk	Attributable proportion (%)
Kansas males (n = 9)	1976–1982	Herbicides	1.6	11
Yorkshire (n = 4)	1979–1984	Fertilizers, herbicides	1.3	4
		Solvents	1.2	4
Wisconsin males (n = 8)	1968–1986	Farming	1.2	4
Nebraska (n = 10)	1983–1986	Herbicides	13.	9

Table 5 *Adjusted incidence of NHL among whites in the United States, 1984–1988*

	Actual 1984–1988 (a)[a]	"New" NHL (b)	HIV (c)	Occupation (d)	Adjusted 1984–1988 (e)
Males	17.4	1.7	0.7	1.5	13.5
Females	11.6	1.2	0	0.5	9.9
Males 75–84	99.5	49.8	0	4.3	45.4
Males 0–64	10.5	0.8	0.8	1.1	7.8
Females 25–34	2.3	0.2	0	0.2	1.9

[a] b, estimated rate of NHL that would have been missed earlier because of diagnostic procedures or classification of NHL. $e = a - (b + c + d)$.

Table 6 *Adjusted[a] NHL incidence rates among whites in the United States*

	1947–1950	1984–1988	Difference	% change
Males	7.5	13.5	6.0	80
Females	5.1	9.9	4.8	94
Males 75–84	21.7	45.4	23.7	109
Males 0–64	5.5	7.8	2.3	42
Females 25–34	2.0	1.9	−0.1	−5

[a] Adjusted for Hodgkin's, new entities, diagnostic change, occupation (see text).

If 10% of NHL among white men was occupation-related in 1984–1988, then 1.5 cases/100,000 person-years would be due to occupation (Table 5). This is equivalent to assuming that 20% of men were exposed in the late 1980s to occupational hazards with an average relative risk of 2.0. We are assuming that 0% were exposed in the late 1940s. It is not clear what portion of NHL among women should be considered a high but reasonable estimate of the proportion attributable to occupation in the general population. If we assume that not more than 10% of white women were exposed to some occupational hazard with a relative risk of 2.0, then 0.5 occupation-related case would have occurred, at most. If 20% of men under the age of 65 were occupationally exposed in the 1980s and the average relative risk of the exposure were 2.0, then 1.1 cases would be occupation-related.

Environmental Exposures

Nonoccupational pesticide exposures have certainly risen, but it is not clear what typical levels of exposure are nor what risks are associated with them. As the data presented by Zahm and Blair (19) show, virtually all agricultural acreage in the United States is treated with herbicide, and the estimated weight of herbicide applied annually has risen from a very low level in the late 1940s to nearly 200,000 metric tons (20).

Hair dyes also have been implicated in NHL, and hair dye use has risen dramatically over the 40-year period. In data from 1980–1983 in Iowa and Minnesota, 4% of NHL in men was linked to hair dye use (21). In 1983–1986 Nebraska data, 20% of NHL in women was linked to hair dyes (22). These associations are much less clearly established than the occupational associations, but it is possible that they contribute to the rising trend.

Perhaps changes in diet, or some concomitant of urbanization, environmental pollution, vaccination levels, or stress have played a role in the rise of NHL. The dietary hypotheses proffered to date concern milk, butter, liver, coffee, and cola (23, 24). For coffee, milk, and meat, the trends in consumption do not parallel the NHL trend. Otherwise, it is impossible to say whether or how much these widespread exposures affect risk.

Conclusions

Table 6 shows that the various factors we have considered here—accuracy and completeness of diagnosis, the impact of HIV, and occupational exposures—leave unexplained an 80% rise in incidence among white men, from 7.5 to 13.5. What levels of risk and changes in prevalence of a behavioral or environmental exposure would be required to explain this increase? An agent (or a level of exposure to an agent) carrying a relative risk of 2.0 would have to rise in prevalence from none to 80% to produce the overall rise in incidence rates. To produce the observed rise among men under the age of 65, an agent carrying a relative risk of 2.0 would have to rise from 0 to 42%. The latter change may not be highly likely, but it is within reason. By contrast, it is hard to imagine an environmental agent to which the entire population is newly and widely exposed that doubles the risk of developing non-Hodgkin's lymphoma.

Perhaps diagnosis or registration has changed vastly more than we posited here. If so, would we expect to see the worldwide increases in NHL? Should those increases have occurred roughly simultaneously or in a pattern suggestive of dissemination of practice? Non-Hodgkin's lymphomas demonstrate remarkable heterogeneity; we may gain insights from considering the trends of particular types of NHL. On the other hand, an agent may increase NHL risk, but not determine which pathway a particular cancer will take. Further study of variations in incidence by time and place should be informative. We also need analytic data on the proposed general environmental agents and susceptibility factors. Although we have learned much about the causes of these lymphomas, we still do not understand fully the rising rates.

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