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Does Chronic Fatigue Syndrome Predispose to Non-Hodgkin's Lymphoma?[1]

Paul H. Levine,[2] Daniel Peterson, Faye L. McNamee, Karen O'Brien, Gloria Gridley, Mary Hagerty, Jane Brady, Thomas Fears, Martin Atherton, and Robert Hoover

Epidemiology and Biostatistics Program, National Cancer Institute, NIH, Bethesda, Maryland 20892 [P. H. L., G. G., M. H., J. B., T. F., R. H.]; Incline Village, Nevada 89450 [D. P., K. O.]; Nevada Cancer Registry, Reno, Nevada 89520 [F. L. M., M. A.]

Abstract

Chronic fatigue syndrome, an illness that frequently is associated with abnormalities of cellular immunity, has been reported anecdotally to be associated with an increased incidence of lymphoid hyperplasia and malignancy. This report describes an initial analysis of population-based cancer incidence data in Nevada, focusing on the patterns of non-Hodgkin's lymphoma prior to and subsequent to well described, documented outbreaks of chronic fatigue syndrome during 1984–1986. In a study of time trends in four age groups, the observed time trends were consistent with the national trends reported in the Surveillance, Epidemiology, and End Results Program. No statistically significant increase attributable to the chronic fatigue syndrome outbreak was identified at the state level. Additional studies are in progress analyzing the data at the county level, reviewing patterns in other malignancies, and continuing to monitor the cancer patterns over subsequent years.

Introduction

CFS[3] is a constellation of signs and symptoms (1) that has received considerable attention (2) and has recently been the subject of a number of reviews (3–6). Although it appears to be comprised of more than one entity with more than one inciting agent (3, 7, 8), the possibility has been raised that CFS predisposes to malignant disease, including NHL (9).[4] One of the more recent clusters of CFS which has received considerable attention was identified in the Lake Tahoe region, initially in Incline Village (7, 8, 10–12), which was noted to have patients with the same abnormalities of cellular immunity (12, 13) and elevated viral antibody titers (8, 12, 14) that have been associated elsewhere with this illness. The physicians first noting the 1984–1986 cluster of CFS patients in Incline Village reportedly observed an unusually high frequency of lymphoproliferative disorders in their practice,[4] and therefore a preliminary review of data from the Nevada Cancer Registry was conducted which suggested an increase in the number of NHL cases coinciding with the apparent outbreak (Fig. 1). The present study was undertaken to determine if the NHL incidence had increased more than expected, given historical trends, and to establish procedures for the evaluation of other possible CFS-related malignancies.

Materials and Methods

Identification of Cancer Cases. All cases reported to the Nevada Cancer Registry have been computerized since 1979. In 1988, a change in Medicare reimbursement policy appeared to result in delayed ascertainment of cases. Therefore, data were only analyzed through 1987.

Statistical Methods. The analysis was intended to determine if any changes in observed NHL incidence after 1984 were consistent with a link between CFS and NHL. The NHL cases for Nevada were ascertained according to 5-year age interval to 85–. Using four age groups, 15–34, 35–54, 55–74, and 75+, Nevada incidence rates were calculated, age adjusting overall and within age group by direct standardization to the 1970 United States population, for comparability.

Using SEER program incidence rates, Devesa and Fears (15) found that since 1970 NHL incidence rates increased among both men and women. They also found that the rate of increase was larger for successively older age groups. We therefore examined the size of recent changes in NHL age group incidence in relation to the long term temporal trends that have been found for NHL.

The secular temporal in NHL incidence in Nevada were estimated in each age group using linear regression of the logarithm of the rates on year, weighted by the number of cases (16). A single dichotomous variable indicating the particular year or years of interest (1984–1987) was added to the model to determine the extent to which the rates for that year or years were not consistent with the modeled secular trends. A significant positive coefficient on the dichotomous variable would suggest an unusually large average increase in NHL rates for the specified year or years. Significance tests were adjusted for multiple comparisons by the Bonferroni correction.

Results

The incidence rates for NHL in Nevada residents between 1980 and 1987 showed temporal trends that were consistent with those in the SEER data (Table 1; Fig. 2). When age-specific incidence rates were examined graphically, the only suggestive increases in incidence subsequent to the CFS outbreak (which peaked in 1985) (6) were in 1984 and 1986, and in the older age groups (35+) (Fig. 3). Based on the regression analyses, however, the general increases in these years were not significant, *i.e.*, they were not inconsistent with the temporal trends in the data. Restricting attention to the age groups most likely to have had exposure to CFS (35–54 and 55–74), a significant increase was again not found. The observed increases in NHL were not inconsistent with the temporal trends in NHL incidence during the period 1980–1987.

Discussion

This study was undertaken because of the report of an increased incidence of cancer associated with an outbreak of CFS (9) and the personal observations of the internists first reporting the Lake Tahoe outbreak, suggesting an unusual frequency of lymphoid hyperplasia and/or malignancy in their practice.[4]

In this early stage of research regarding a potential link between CFS and cancer, two hypotheses are of primary interest. The first is that an infectious agent, probably a virus, is responsible for the outbreak of CFS, which is the predominant clinical manifestation, but in other cases there is subclinical immunosuppression that results in malignancy in others involved in the "cluster." Such a hypothesis has been proposed by Grufferman *et al.* in their study of a 1984 outbreak in a North Carolina symphony orchestra (9), where immunological abnormalities and an increase in cancer cases (observed/expected = 18.2, 95% confidence interval = 5.0–46.7) was apparent in the 3 years

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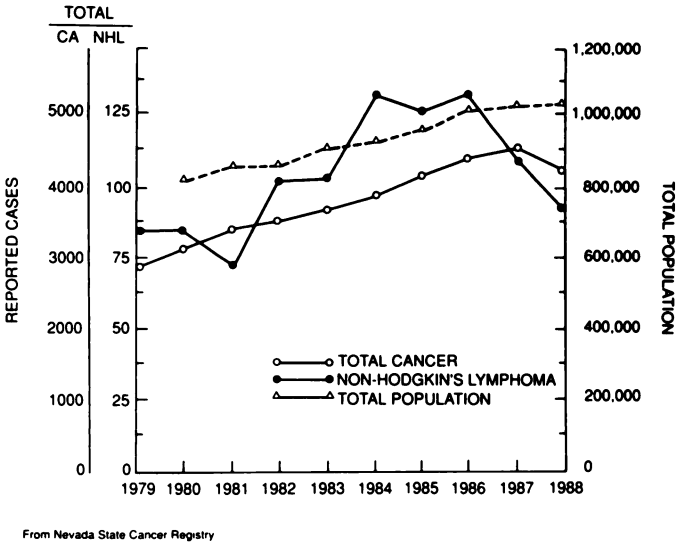
[2] To whom requests for reprints should be addressed, at Executive Plaza North, Room 434, Bethesda, MD 20892.

[3] The abbreviations used are: CFS, chronic fatigue syndrome; NHL, non-Hodgkin's lymphoma.

[4] D. Peterson and P. Cheney, personal communication.



From Nevada State Cancer Registry

Fig. 1. Cases of cancer (*CA*) and NHL: 1979–1988. Total number of cancer cases and NHL cases reported to the Nevada Cancer Registry between 1987 and 1988 in comparison with the entire Nevada population.

Table 1 *Nevada state age-specific NHL rates*[a]

Year	No. of NHL cases observed	Rates by age group				Total rate
		15–34	35–54	55–74	75+	
1980	68	1.081	6.372	25.019	24.582	7.397
1981	54	0.569	5.696	18.336	31.837	5.978
1982	95	3.458	11.004	31.454	38.107	9.843
1983	92	1.158	9.341	32.034	52.958	9.590
1984	113	2.681	9.800	37.517	79.077	12.340
1985	76	1.138	8.524	24.747	37.426	7.448
1986	118	1.762	11.924	40.979	62.160	11.661
1987	92	1.781	7.358	30.911	56.809	8.895

[a] Per 100,000 population (age adjusted to United States 1970 population).

(1984–1987) associated with the CFS outbreak. The immunological abnormalities occurred in clinically unaffected contacts as well as CFS cases and were identified as late as 1987, 3 years after the outbreak. As discussed earlier (3, 7), such outbreaks are unlikely to result from infection with EBV or HHV-6, two CFS-associated viruses which have been associated with lymphoid malignancies (17–20), because they are endemic in all United States populations. Virtually everyone is immune by age 15, and outbreaks of illness from these viruses are unlikely. A novel agent, such as described in the report by DeFreitas *et al.* (21), however, could provide such a pattern.

The second hypothesis is that malignancy is a subsequent outcome of the immunological dysregulation associated with CFS. While there is no specific laboratory test for CFS, most investigators note an abnormality of cellular immunity (3, 12, 13, 22), the most consistent being a decrease in natural killer cytotoxicity (22–24) which appears to be important in protecting against cancer (25).

Our evaluation of the Nevada Cancer Registry data for this report, while very preliminary, may be useful as a basis for evaluating more anecdotal reports of associations between CFS and cancer. The inclusion of the entire state in this study is justified because CFS was observed in Yerington and other areas in northern Nevada (7, 8, 10–12) as well as in Incline Village. In subsequent analyses, we will focus more on the comparison of counties. Our initial evaluation of 1984–1987 is important because it parallels the precise time periods where Grufferman *et al.* reported a possible increase in cancer incidence (including NHL) associated with a CFS outbreak in North Carolina. Our findings thus far do not support such an association and Grufferman also has subsequently noted that these findings have not been confirmed in other outbreaks he has investigated (26).

Furthermore, since some forms of NHL, particularly Burkitt's lymphoma, have been estimated to have a latent period of less than 1 year (27, 28), and latent periods less than 6 months have been observed in transplant patients (29), evaluation of this short latent period is of considerable importance. In general, however, a longer latent period between exposure to an environmental carcinogen and the subsequent appearance of NHL is suspected.

Overall, our data do not indicate that CFS leads to an increase in NHL within 3 years of an "outbreak." The only data requiring further pursuit are the suggestive increases in the older age groups (35+) in 1984 and 1986. To further resolve the issue of the alleged relationship between CFS and cancer, it is important to continue to monitor the state of Nevada, analyze data by county as well as statewide, look into histological

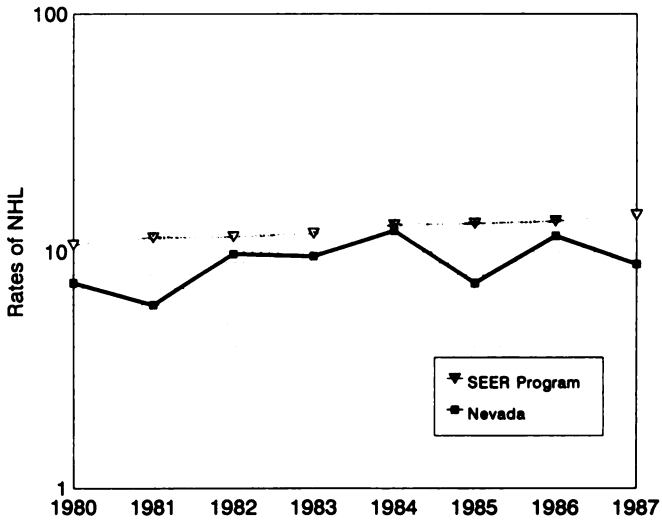


Fig. 2. Incidence rates per 100,000 for NHL, all ages, from the Surveillance, Epidemiology, and End Results (*SEER*) Program and the Nevada Cancer Registry, age adjusted to 1970 United States standard population.

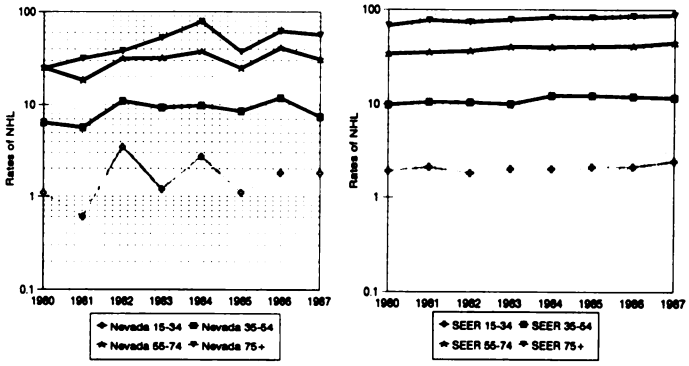


Fig. 3. Incidence rates per 100,000 for NHL in the Surveillance, Epidemiology, and End Results (*SEER*) Program (excluding San Francisco) and the Nevada Cancer Registry age adjusted within age groups to 1970 United States standard population.

subtypes of lymphoma and other malignancies, and consider different latent periods for different forms of cancer. These studies are in progress.

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Discussion

Dr. Levy: I'm particularly interested in the low-grade lymphomas that Dr. Levine sees in AIDS[1] patients. Are any of those follicular lymphomas? And if so, what does their circulating CD-4 count look like?

Dr. A. Levine: First of all, I have to just back up a little bit. L.A. County Hospital serves an indigent population. I've never seen this published, but we don't see very much follicular lymphoma.

What we see is diffuse small cleaved. On the other hand, I believe I've seen two cases of follicular small cleaved in HIV-infected patients. Most of them had not very high-grade T-cells, but not low—in other words, in the normal range.

Dr. Levy: The reason I asked the question is because I have a theory about follicular lymphoma based on CD-4 T-cell stimulation of lymphoma growth. Of course, if you had cases where CD-4 cells were depleted and they were getting follicular lymphoma, that would disprove my theory.

Dr. Banks: Dr. Levine, I'm not sure I understood your data correctly with the AZT-treated cohort of HIV-positive patients. Do I understand correctly that with increasing time, beyond the point there was no additional incidence of lymphoma?

[1] The abbreviations used are: AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus; AZT, 3′-azido-3′-deoxythymidine; EBV, Epstein-Barr virus; NHL, non-Hodgkin's lymphoma; 2,4-D, (2,4-dichlorophenoxy) acetic acid.

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