

An Approach to Studies of Cancer Subsequent to Clusters of Chronic Fatigue Syndrome: Use of Data from the Nevada State Cancer Registry

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Chronic fatigue syndrome (CFS) has been increasingly associated with immune dysregulation, including depressed natural killer cell activity; this phenomenon is associated with increased susceptibility to cancer. Although anecdotal reports have suggested an association between CFS and cancer, particularly non-Hodgkin's lymphoma and brain cancer, there has been no a priori justification for evaluating such an association and no consideration of relevant parameters, such as length of latent period vs. tumor type. We reviewed data from the Nevada State Cancer Registry subsequent to a reported outbreak of a CFS-like illness in Nevada that occurred during 1984–1986. We concentrated on non-Hodgkin's lymphoma and brain/CNS tumors, with particular emphasis on persons 15–34 and 35–54 years of age. An upward trend in the incidence of brain/CNS tumors, which could be related to a national upward trend for this disease, was noted. No consistent trends were noted for non-Hodgkin's lymphoma. Because of the difficulties inherent in studies of cancer subsequent to various exposures, we evaluated the methodology for determining an association between outbreaks of CFS-like disease and cancer. We propose several approaches that should be considered in future studies for investigation of possible associations between CFS and cancer, including expected latent periods for specific tumors.

Results of laboratory studies indicate that many patients with chronic fatigue syndrome (CFS) have abnormal lymphocyte function, including depressed natural killer (NK) cell activity [1–7]. These abnormalities have been described in case series [1–4] as well as in reports of clusters of CFS [3, 5–7]. Depression of NK cell activity has been postulated as being the cause of four cases of cancer associated with a cluster of cases of "chronic fatigue-immune dysfunction syndrome" among members of a symphony orchestra [8]. These four cases included a brain malignancy and a non-Hodgkin's lymphoma (NHL); all cases were diagnosed within 3 years of the onset of CFS in the first patient. Some of the shortest latent periods between exposure and development of a malignancy occur in association with immunodeficiency. Transplant recipients are at high risk of developing lymphomas within months of the procedure and initiation of immunosuppressive therapy [9]. The other malignancies that occur excessively in transplant recipients do not become evident until 3 years after transplantation, and thereafter the risks tend to rise with increasing latency.

Thus far, no data bases have been developed to investigate possible associations between CFS or CFS-like outbreaks and cancer. Without such data bases, the reports of cancer

associated with CFS clusters are impossible to evaluate. Therefore, because of the occurrence of a well-described CFS-like illness in Nevada [5, 7, 10–12], a state with an established cancer registry, we undertook a systematic study of the pattern of cancer cases with use of data collected by the Nevada State Cancer Registry (NSCR). In this report we expand on our initial analysis of the pattern of NHL in Nevada [13] by including data on brain tumors and review some of the methodological problems that must be considered in attempting to determine if outbreaks of CFS are associated with a significantly increased risk of developing cancer.

Materials and Methods

The NSCR is a population-based tumor registry established in 1979. It currently includes roughly 38,000 cases of invasive cancer diagnosed and treated in hospital facilities throughout Nevada. Incidence and survival rates can be calculated based on data from these accessioned cases with use of statewide population estimates derived from the decennial census.

All cases of invasive cancer are ascertained using hospital patient records, disease indexes, death records, pathology reports, and other pertinent medical documents that contain information related to health and vital status. On the basis of criteria for registry completeness (in accordance with accreditation standards of the American College of Surgeons), it is estimated that the NSCR identifies between 90% and 95% of all invasive-tumor cases that come to the attention of medical facilities in Nevada within a 1-year period. More recently

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the NSCR has identified invasive-tumor cases diagnosed and treated at outpatient clinics and facilities. Because of the remoteness of some cancer-treating facilities in Nevada, a small percentage (i.e., <10%) of cancer cases are accessioned only once every 2 years; other cases are accessioned via sharing of cancer-registry data with states in which patients from Nevada receive diagnoses and treatment as nonresidents. No more than 20% of all cancer cases are accessioned >2 years after initial diagnosis at a treatment facility. Roughly 4,300 new cases of invasive cancer are diagnosed and accessioned into the NSCR each year. For the purposes of this study, a case refers to a single primary tumor and not an individual.

The analytic approach used for this report was the same as that used in our initial study of NHL [13]. Based on the short latent period between immunosuppression and the development of cancer, as documented for transplant recipients [9] and postulated for CFS [8], this analysis was intended to determine if there were any increases in cancer incidence between 1984 and 1987 that could be associated with the outbreak of CFS that occurred during 1984–1986 in Nevada. For this analysis we compared the data on NHL and brain/CNS cancers (designated as candidate CFS-related malignancies) with those on all cancers (designated as non-CFS-related malignancies). The inclusion of multiple myeloma and other lymphoproliferative diseases in the 10th version of the International Classification of Diseases-Oncology required reanalysis of the NHL data we published previously [13]. The cases for Nevada were ascertained according to patients' ages in 10-year intervals up to 85 years. Population estimates provided by the Nevada Center for Health Statistics were used to obtain 10-year age-specific incidence rates; four age groups (15–34, 35–54, 55–74, and >75 years) were used to calculate incidence rates, which were adjusted within each group by direct standardization to the 1970 United States population.

We examined the Nevada incidence data with use of weighted linear regression of the logarithm of the age-adjusted rates, with the observed number of cases as weights. Age groups were omitted from the regression if the corresponding number of cases was small. The secular trends in incidence were estimated using regression on year. To determine the extent to which the rates for a particular year or group of years were consistent with the modeled secular trend, a single dichotomous variable indicating the year(s) of interest was added to the model. A significant positive coefficient associated with a dichotomous variable suggested an unusually large relative increase in rate for the specified year(s). Significance tests were one-sided, and *P* values were adjusted for the number of comparisons with use of the Bonferroni correction [14] by site, i.e., multiplied by three.

Results

Counts and age-adjusted rates for both sexes combined are provided in table 1 for the four age groups, for the two study malignancies, and for all sites combined.

Particular emphasis was placed on those age groups (i.e., 15–34 and 35–54 years) that included patients most likely to have CFS. Results are summarized in figure 1. The annual relative increase in rates of brain/CNS cancer was 5.4% per year ($P = .09$) and did not differ significantly between the two age groups. The fit is satisfactory. Rates for 1984 and 1985 are 10%–30% below the trend line, and those in 1986 are below or on the line; the differences are small and variable. After correction for multiple comparisons, deviations are not statistically significant for any single year or for the interval 1984–1986.

The annual relative change in NHL rates for these age groups is negative at –2.3%, not significant ($P = .54$), and does not differ between the two groups. The fit is satisfactory. Rates in 1984 are 20% above the trend line but ~14% below the line in 1985; the differences are small and variable. Relative deviations are not statistically significant for 1984, 1985, 1986, or the interval 1984–1986.

The annual relative change in rates for all sites is negative and differs by age group: –5.7% and –1.3% for those 15–34 and 35–54 years, respectively. Patterns are not discernable, and relative deviations are not statistically significant for 1984, 1985, 1986, or the interval 1984–1986.

When all four age groups rather than just those age groups most likely to have had CFS are considered, trends in brain/CNS malignancies are positive for each of the four age groups. In 1985, rates were below the trend for younger age groups and above the trend for older age groups. In 1986 and 1987, brain/CNS malignancy rates were generally below the trend. Changes are not statistically significant for any single year or for the interval 1984–1986. The trends in NHL rates seem to differ in relation to age group, with the slope increasing with increasing age—negative for the younger ages to positive for the older ages. Rates are ~20% above the trend line in 1984, 15% below the trend in 1985, and ~18% above in 1986. These differences are small and variable. Changes are not statistically significant for any single year or for the interval 1984–1986. For all sites, the trends clearly differ by age group, patterns are again not notable, and relative deviations are not statistically significant for 1984, 1985, or 1986 or for the interval 1984–1986.

Thus, observed changes in cancer rates for the years 1984, 1985, 1986, and 1984–1986 with regard to the study malignancies were not inconsistent with temporal trends in the incidence during the period 1981–1987.

Discussion

An association between CFS and cancer, of potential significance because of the abnormal cellular immunity pattern seen in many patients with CFS [1–7], has been suggested based on observations involving one reported CFS cluster [8]. As noted in studies involving “cancer clusters” [15], however, anecdotal reports can be the result of inadvertent manipulation of the geographic areas under analysis to fit the

Table 1. Age-specific cancer rates in Nevada per 100,000 population (age-adjusted to United States 1970 population).

| Type of cancer | Age of patients (y) | | | | | | | |
|--------------------|---------------------|-----|--------|-----|---------|------|---------|-----|
| | 15-34 | | 35-54 | | 55-74 | | >75 | |
| Brain/CNS | | | | | | | | |
| Year | | | | | | | | |
| 1981 | 2.21 | 7 | 8.85 | 17 | 22.08 | 29 | 17.62 | 4 |
| 1982 | 2.94 | 9 | 7.52 | 14 | 18.62 | 26 | 16.17 | 4 |
| 1983 | 2.25 | 8 | 8.73 | 19 | 20.94 | 30 | 26.53 | 7 |
| 1984 | 1.57 | 6 | 7.11 | 15 | 22.19 | 33 | 32.89 | 9 |
| 1985 | 2.62 | 10 | 6.73 | 15 | 19.46 | 30 | 20.90 | 6 |
| 1986 | 3.12 | 11 | 7.80 | 18 | 23.00 | 37 | 41.35 | 13 |
| 1987 | 4.48 | 17 | 10.81 | 27 | 18.82 | 32 | 11.74 | 4 |
| NHL* | | | | | | | | |
| Year | | | | | | | | |
| 1981 | 1.04 | 4 | 9.21 | 17 | 31.14 | 41 | 68.70 | 15 |
| 1982 | 3.19 | 10 | 13.92 | 28 | 38.96 | 54 | 65.51 | 16 |
| 1983 | 2.54 | 8 | 10.02 | 20 | 41.76 | 60 | 80.81 | 21 |
| 1984 | 2.68 | 10 | 13.33 | 28 | 45.05 | 67 | 99.08 | 27 |
| 1985 | 1.08 | 4 | 10.74 | 25 | 42.16 | 65 | 54.39 | 16 |
| 1986 | 1.72 | 7 | 13.43 | 31 | 46.75 | 75 | 95.71 | 30 |
| 1987 | 1.66 | 7 | 8.61 | 21 | 35.48 | 60 | 80.03 | 27 |
| All cancers | | | | | | | | |
| Year | | | | | | | | |
| 1981 | 63.90 | 217 | 365.55 | 695 | 1434.71 | 1881 | 2812.48 | 627 |
| 1982 | 65.32 | 232 | 366.29 | 729 | 1452.81 | 2013 | 2644.76 | 643 |
| 1983 | 56.82 | 204 | 350.19 | 714 | 1516.57 | 2178 | 2781.16 | 720 |
| 1984 | 55.83 | 203 | 322.95 | 676 | 1570.52 | 2336 | 2776.42 | 764 |
| 1985 | 53.02 | 198 | 349.32 | 763 | 1637.90 | 2529 | 2818.73 | 823 |
| 1986 | 41.37 | 164 | 338.85 | 772 | 1681.83 | 2697 | 2788.00 | 864 |
| 1987 | 50.50 | 201 | 340.30 | 812 | 1634.57 | 2752 | 2783.45 | 926 |

NOTE. Figures in left-hand column under each age group represent number of cases per 100,000 population; figures in right-hand column represent total number of cases.
 * NHL = Non-Hodgkin's lymphoma.

reported cases. Therefore, large numbers of individuals at risk are required for documentation of an association, and the areas of study should be defined before analysis, rather than after. The NSCR data offered a model for evaluating the occurrence of cancer following a reported cluster of CFS cases similar to that affecting the symphony orchestra in the early reports, in which cancer was associated with chronic fatigue-immune dysfunction syndrome [6, 8].

Since the initial approach to the analysis was to attempt to replicate the findings of the symphony-orchestra study, we designated the latent period in our study (the period between the occurrence of the precipitating event [CFS] and alleged secondary outcome [NHL and brain tumors]) as 3 years, which was the same period as the interval between the initial identification of CFS cases among members of the symphony orchestra and the appearance of cases of NHL and brain cancer [8]. As in the earlier report, we tested the hypothesis that the cluster occurred in a population affected by a new agent that resulted in low NK cell activity; the outcome was CFS for some individuals and malignancy for others, with concurrence of the two conditions less common. The analy-

sis of the statewide data up to 1987 did not identify any statistically significant upward change in pattern that demonstrated a significant difference between the period 1984-1986 and the entire period 1981-1987. While there was an increase in the occurrence of brain tumors, this increase did not significantly exceed the time trend. A major difficulty in the analysis is that while many people have been exposed to the putative agent causing the apparent cluster, many were probably not exposed, and the exact numbers are unknown. The power of the study is therefore unknown but is probably not strong.

As noted above, a primary purpose of this report is to review specific issues that arose during our consideration of a causal vs. casual relationship between cancer and CFS. Our approach was particularly intended to address clusters of CFS, but the issues are pertinent to evaluation of sporadic cases as well. Specific questions that need to be considered are as follows:

- (1) What is the likely incubation or latent period for each tumor under evaluation?

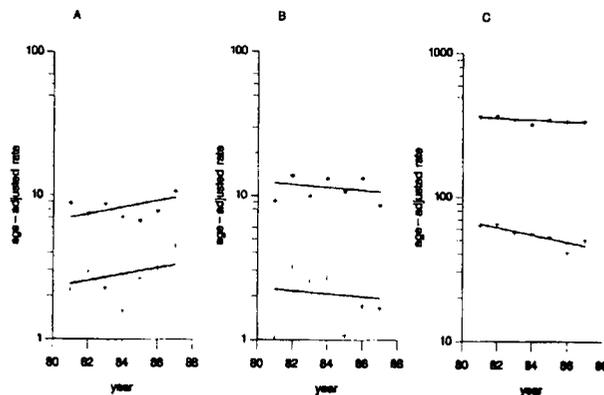


Figure 1. Annual incidence rates per 100,000 for brain/CNS cancers, non-Hodgkin's lymphoma, and all other cancers recorded in the Nevada State Cancer Registry. Adjustment for age was made within age groups according to the 1970 standard. Secular trends are represented with solid lines; + = ages 15-34; * = ages 35-54.

Specific data exist regarding latent periods between exposure to the etiologic agent and subsequent malignancy, and while not necessarily referable to CFS, they do provide a starting point. Data on transplant recipients that document a short latent period for lymphomas and longer latent periods for other malignancies [9] are informative. Radiation-associated malignancies provide another model for estimating relative length of latent periods. For example, acute lymphocytic leukemia occurs 2-3 years after acute exposure to radiation, and breast cancer, >10 years after exposure [16].

In any epidemiologic study, two independent factors need to be considered in proposing the probable interval between precipitating event and the subsequent appearance of a malignancy: the latent period, as discussed above, and the doubling time of the tumor. Data on time-space clusters of Burkitt's lymphoma [17-19] are more plausible than those for carcinomas because of the rapid doubling time of the former tumor, estimated at 24 hours.

In the symphony-orchestra cluster, Grufferman et al. [8] noted one case of lymphoma and one case of breast cancer in two CFS-affected orchestra members and a brain tumor and a parotid tumor in two non-CFS contacts. If one considers the doubling time of carcinoma cells and the long latent period between exposure to reported etiologic agents and breast malignancy [16], however, it is difficult to implicate a relationship between CFS and this case of breast malignancy. In general, since breast cancer is a common neoplasm and the occurrence in a cluster of diverse neoplasms is likely to be coincidental, it would be appropriate for systematic studies such as ours to concentrate on less-frequent illnesses that are more likely to be related to the immune system.

(2) What malignancies are likely to result from a CFS-associated immune disorder?

Three important features of the cancer risks among transplant recipients and other populations with altered immu-

nity are noteworthy in this context. First, there is no general diathesis related to malignancy. Rather, only a limited number of cancers, particularly NHL, are excessive, and the type of malignancy is dependent on the specific immune defect [20]. While there are sporadic reports of excesses of some other tumors, including bladder cancer and adenocarcinomas of the lung and stomach, it is noteworthy that evidence of excesses of some of the more common malignancies (e.g., breast and colon cancers, and squamous-cell lung cancer) is lacking.

Second, the cancers most clearly associated with altered immunity are ones that are most likely to have a viral etiology, such as NHL (Epstein-Barr virus) and hepatocellular carcinoma (hepatitis viruses). Thus, the increased risks observed in relation to fairly short latent periods might be consistent with loss of immunologic control over oncogenic viruses already present within the target cells. If immunologic perturbation increases risks for other malignancies through other mechanisms, these mechanisms have not yet been noted in cancer studies that cover the 10-year latent periods.

Finally, excessive occurrence of cancer in groups with altered immunity are related to the severity of the immune defect. For example, persons infected with the human immunodeficiency virus and patients with sicca syndrome are not at abnormal risk for developing cancer until the immunologic aberration becomes advanced. Thus, as indicated above, if milder alterations in immunity are associated with abnormal cancer risks, these risks would have to occur beyond the latent periods currently assessed for these milder conditions.

(3) Can the findings from one study necessarily be extrapolated to another?

It is increasingly apparent that there is heterogeneity among clusters, as has been well described in this symposium and elsewhere [10, 21, 22]; this finding suggests that the environmental trigger and/or the degree of its effect on the immune system may not be similar among all clusters. Therefore, the findings in one cluster may not necessarily be extrapolated to other clusters.

One consideration relevant to this analysis that was raised by earlier reports from the NSCR [23] was the possibility that exposure to radiation, which was reported to peak during the years 1951-1958, could account for the increase in malignancies. Radiation exposure from atomic testing is a basis for compensation in Nevada [23], although evidence for a cause-and-effect relationship in this context is unproven. From 1980 to 1988 (a period that includes the years encompassed by this study) the incidence rates of radiation-associated cancer were lower than or equal to the national average [23]. Further evaluation of the potential effects of radiation and/or CFS in the Nevada population will be feasible when data by county are analyzed since the radiation exposure was more apparent in southern Nevada, and CFS was more prominent in the northern part of the state.

In summary, there are several important considerations with regard to the interpretation of data from this and future studies:

(1) Each CFS cluster may be due to a different precipitating agent, and a different group with different susceptibilities to cancer may be involved. Therefore, the inferences derived from one CFS cluster may not be validly applied to another.

(2) "Outbreaks" of CFS may not be the same illness as sporadic cases of CFS. Not only are the precipitating agents likely to be different [10], but as noted elsewhere in this symposium [22], not all affected patients meet the current case definition of CFS. Therefore it is not clear that outcomes reported in outbreaks of CFS are relevant to sporadic cases of CFS.

(3) Depressed NK cell activity and other abnormalities of cellular immunity are not a uniform finding in CFS, and since this is the proposed mechanism for the development of cancer, not all patients with CFS may even be susceptible to malignancy. Furthermore, it is clear that different immune disorders are associated with different malignancies [20].

(4) Trends in cancer incidence should be considered in analyzing specific CFS cohorts. Brain tumors, chosen for this analysis because of the unusual clustering noted by the private-practice physicians involved in the Lake Tahoe cluster (D. Peterson, personal communication), are difficult to evaluate because of the increasing nationwide trend [24], which has also been observed for NHL [23, 25]. Because of the stronger upward trend in cases of brain/CNS cancer than in NHL, however, future studies of an association of CFS and cancer should emphasize brain/CNS malignancies as a candidate CFS-related outcome.

Our study of statewide incidence of cancer associated with the 1984-1986 outbreaks of CFS reported in the northern part of Nevada thus far has yielded no specific link between CFS and any particular malignancy. To date, a link between CFS and cancer is tenuous and relies solely on anecdotal data. The association can be evaluated scientifically, but appropriate studies will require large numbers of patients and specific biologically plausible hypotheses. Studies for approaching this question are now being developed.

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