



# Cancer and a Fatiguing Illness in Northern Nevada—A Causal Hypothesis

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**PURPOSE:** We investigated the possibility that chronic fatigue syndrome (CFS) predisposes to cancer by comparing the cancer pattern in an area in northern Nevada, where an outbreak of a fatiguing illness, which included cases of CFS, was reported, to an area in southern Nevada, where no such illness was reported.

**METHODS:** Data from the computerized Nevada Cancer Registry were utilized to compare incidence rates of four malignancies—brain cancer, non-Hodgkin lymphoma (NHL), lung cancer, and breast cancer—in Washoe and Lyon Counties, where an unexplained fatiguing illness was reported during 1984–86, with comparably sized Clark County, where no such illness was reported.

**RESULTS:** Higher incidences of NHL and primary brain tumors were noted in the two northern Nevada counties (Washoe and Lyon) in 1986 and 1987 respectively, compared to the southern Nevada (Clark) county. Similar patterns were not seen for breast or lung cancer.

**CONCLUSIONS:** This study provides a model for investigating the possible predisposition of CFS patients to develop cancer using other cohorts, but it is currently premature to accept such a link at this time.

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**KEY WORDS:** Chronic Fatigue Syndrome, Epidemic Neuromyasthenia, Natural Killer Cells, Non-Hodgkin Lymphoma.

## INTRODUCTION

Chronic fatigue syndrome (CFS) is a debilitating illness that is associated with a number of symptoms including cognitive disorder, tender lymph nodes, migratory arthralgias, headache, and sleep disorders (1, 2). No consistent laboratory abnormality has been identified but a significant number of patients have immunologic dysregulation, including moderately decreased natural killer (NK) cell activity (3–6), which in animal systems is associated with an increased susceptibility to cancer. Stimulated by this and the reports of an apparent excess of cancer associated with an outbreak of CFS in a symphony orchestra (7, 8), we have been investigating whether or not there is an increase in malignancies subsequent to CFS, particularly attempting to evaluate defined populations. Between 1984 and 1986, there was an apparent outbreak of an infectious disease in northern Nevada/California characterized by prolonged fatigue and many of the signs and symptoms associated with CFS (9–11). There was no evidence of a similar outbreak reported

from southern Nevada although fatiguing illnesses are not reportable. The reported cluster of cases in northern Nevada/California resembled previous reported clusters of fatiguing illness, often referred to as epidemic neuromyasthenia (EN) (12–14), which included cases that clearly met the subsequently published case definition for CFS (11, 15, 16).

In earlier work, we considered a possible link between CFS and cancer during the reported outbreak of CFS-like illness in northern Nevada using data from the Nevada Cancer Registry and concentrated on NHL (17) and brain tumors (18). These particular tumor sites were selected because of anecdotal reports of lymphoid and brain tumors from the physicians who first noted the increase in their patients involved in the reported outbreak in 1986, Drs. Daniel Peterson and Paul Cheney. In our earlier studies, which used state-wide data (17, 18), we noted methodologic problems, including the lack of a hypothesis regarding the latent period between the putative infection with a causative agent and the subsequent appearance of a malignancy. Although some increases in Nevada NHL and brain tumors were noted in our original reports, the increases were not considered significantly different from the trends after correction for multiple comparisons; thus, evidence of a relationship between the outbreak of the fatiguing illness and malignancy was not considered strong.

In this study, we take a different approach to the question

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**Selected Abbreviations and Acronyms**

CFS = chronic fatigue syndrome  
 NHL = non-Hodgkin lymphoma  
 EN = epidemic neuromyasthenia

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by comparing cancer patterns in the two northern Nevada counties in which the outbreak was reported with those in a southern Nevada county in which no unusual reports of a fatiguing illness were noted. The rationale is that while our first studies considered all of Nevada and had the advantage of relatively large numbers, not all of the state experienced an outbreak, and this may have diluted any apparent effect resulting in reduced power for these studies.

By comparing counties with the reported fatiguing illness to apparently unaffected counties we can, to some extent, avoid this problem, but, because the study cancer sites are rare, the number of cases observed is small and power is still weak.

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**MATERIALS AND METHODS**
**Cancer Incidence**

Data from the Nevada Cancer Registry have been computerized since 1979. The data analyzed for this study included Nevada residents of all races, aged 25 to 54, for NHL, brain, breast, and lung cancer in Washoe and Lyon counties, which reported EN cases in 1984 to 1986; and in Clark County, a county apparently not affected by the outbreak.

We compared the cancer incidence rates in the Washoe and Lyon counties with Clark county. Washoe, which includes Reno, and Clark, which includes Las Vegas, are the most heavily populated counties in Nevada. Lyon is much smaller and not as heavily populated. All three counties are predominantly White, each has a notable Hispanic popula-

tion but only Clark has a sizable Black population. Lyon has the largest proportion of family households, but houses cost substantially less.

We used Poisson regression (19) to study incidence rates for both sexes during the years 1980 to 1990 for NHL, and brain, lung, and breast cancer. The age groups studied, ages 25 to 54, were those most affected by the outbreak. NHL and brain cancer were hypothesized target sites based on literature reports. We considered breast cancer and lung cancer rates as a negative control to be certain that findings were not simply part of a general pattern.

The outbreak of fatigue is believed to have occurred during the years 1984, 1985, and 1986. These years are here referred to as the exposure years while 1987 through 1990 are referred to as after exposure years. Adjusting for 10-year age group we estimated the rate ratio for outbreak counties against the non-outbreak county for each of the 11 years. Our analysis then proceeded in two steps. First we considered if there was a difference in rate ratios for the years before exposure, the years during exposure and the years after exposure. If such a difference was suggested by the data then we considered other hypotheses. We looked at rate ratios for individual years. We examined the effects to see if rate ratios increased with exposure and again after exposure. We also considered the hypothesis that the rate ratio was different only in the years after exposure and if so whether it increased. We did not require statistical significance at the first step but only that differences be suggestive. Use of such a two stage procedure is one way to address concerns about multiple comparisons and spurious positive results.

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**RESULTS**

The incidence of NHL, both sexes, age groups 25 to 54 in Washoe and Lyon counties where the incidence of cases of fatigue was reportedly high, was compared with that of Clark

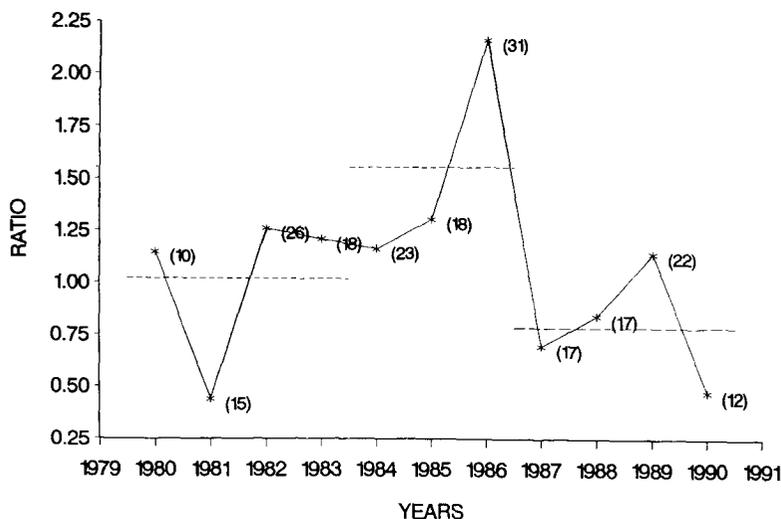


FIGURE 1. Estimated ratios of NHL rates for Washoe-Lyon/Clark by year and CFS exposure categories adjusted for age, both sexes, ages 25 to 54.

**TABLE 1.** Estimated constant rate

Period	Years	NHL	Brain	Breast	Lung
Pre-outbreak	1980-83	1.0	0.9	1.0	1.0
Outbreak	1984-86	1.6	1.0	0.9	0.9
Post-outbreak	1987-90	0.8	1.4	1.1	0.9

county, where it was not. The ratio of NHL incidence rates in Washoe and Lyon counties to Clark county was estimated for each year between 1980 and 1990 adjusting for 10-year age group. These estimates are plotted with a solid line in Figure 1 along with the total number of cases used in the estimate. The rates are based on small numbers of cases so the estimated rate ratios are erratic but the value in 1986 is notable. The rate ratio was modeled with one constant during the years prior to the outbreak; a second constant during the years 1984 through 1986 when the outbreak occurred, and a third constant for the years after the outbreak (see Table 1). The estimated constant rate ratios, 1.0, 1.6, and 0.8 for before, during, and after the outbreak, are plotted with a dashed line. The model had a *P* value of 0.08 and the change associated with the years during the outbreak had a *P* value of 0.07. The ratio in 1986 is estimated to be 2.2 and differs from other years with a *P* value of 0.02. All *P* values are two sided.

Comparing incidence rates for brain cancer, both sexes, ages 25 to 54 in Washoe and Lyon counties with those in Clark county, the Poisson regression estimates of the rate ratios for each year between 1980 and 1990 are similarly plotted in Figure 2. The rate ratios are high beginning in 1985 and particularly high in 1987. The rate ratio was again modeled with one constant during the years prior to the outbreak; a second constant during the years 1984 through 1986 when the outbreak occurred; and a third constant for the years after the outbreak. The estimated constants, 0.9, 1.0, and 1.4 for before, during, and after the outbreak, are

plotted with a dashed line. The model had a *P* value of .24 and the change associated with the years after the outbreak had a *P* value of 0.10. A simple trend tests was not significant (*P* = 0.32). The ratio in 1987 is estimated to be 2.2 and differs from other years with a *P* value of 0.03.

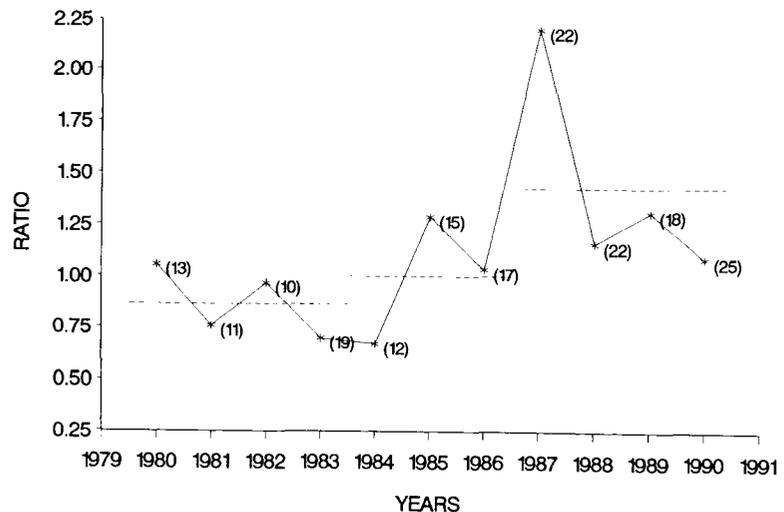
Considering breast cancer, females only, ages 25 to 54 in Washoe county compared to Clark county, the number of cases is large compared to that for the other study cancers and power is therefore relatively large. The estimated rate ratios for Washoe and Clark county for each year between 1980 and 1990 are plotted with a solid line in the Figure 3. The estimated constants, 1.0, 0.9, and 1.1 for before, during, and after the outbreak, are plotted with a dashed line. The model had a *P* value of 0.24. The change after the outbreak had a *P* value of 0.17. The ratio in 1987 is estimated to be 1.1 and differs from other years with a *P* value of 0.17.

For lung cancer, both sexes, ages 25 to 54 in Washoe, Lyon, and Clark counties, no difference between outbreak-related and non-outbreak-related counties were suggested (Figure 4).

## DISCUSSION

This study suggests that in northern Nevada, which was apparently affected by an outbreak of an unexplained fatiguing illness in 1984 to 1986, relatively high incidences of NHL and brain cancer occurred near the end and just following the outbreak. The significance of the increase in brain tumors appears to be more important than the NHL peak, but in spite of these striking post-cluster peaks, this should not be considered a definitive study. First, the rates are based on few cases and are therefore erratic. Second, our hypotheses came from those in the field who were most aware of what was happening in the affected counties. Third, many comparisons were of interest and to some extent most

**FIGURE 2.** Estimated ratios of brain cancer rates for Washoe-Lyon/Clark by year and CFS exposure categories adjusted for age, both sexes, ages 25 to 54.



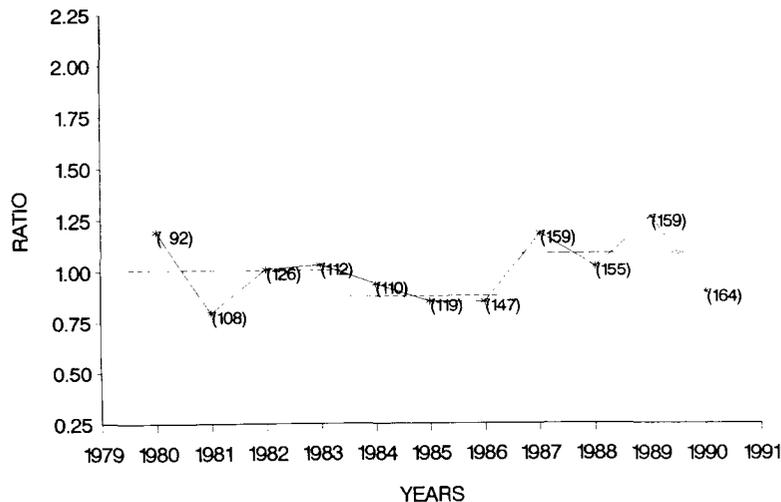


FIGURE 3. Estimated ratios of breast cancer rates for Washoe-Lyon/Clark by year and CFS exposure categories adjusted for age, females only, ages 25 to 54.

were considered. The possibility of a chance positive outcome is therefore still high. Our results should therefore be considered as a hypothesis to be confirmed in independent studies. The observed pattern, however, is biologically plausible. The early peak of NHL is consistent with the pattern observed in transplant patients, where NHL can occur in the first weeks after onset of immunosuppression (20). Brain tumors, which generally grow more slowly than aggressive NHL, are still significant clinical problems, unlikely to be missed, and plausibly peaking within two years of an outbreak of infection apparently associated with immune dysregulation (3).

It is reasonable to consider EN as a phenomenon which is associated with an increased incidence of CFS that appears to be a complex disorder affecting the central nervous system and musculoskeletal system. In addition, CFS also has a number of systemic effects apparently associated with neuro-

endocrine and immunologic abnormalities (3-5, 21). The variety of manifestations and the differences in patterns observed by various investigators indicate that it is a heterogeneous group of disorders currently included under one case definition. Current evidence indicates that CFS is not contagious but can be triggered by a number of different infectious and noninfectious agents, some of these having a higher "attack rate" resulting in increased reports of CFS. Because of the variety of apparent etiologic agents, CFS also being noted in association with sick building syndrome and noninfectious environmental agents, it is not possible to extrapolate the findings from one reported outbreak to clusters occurring elsewhere in the United States. We chose to use this particular cluster as a model for studies which could then be applied to case series of CFS, as well as other reported outbreaks, because of the number of investigators evaluating the Lake Tahoe cluster (9-11), including labora-

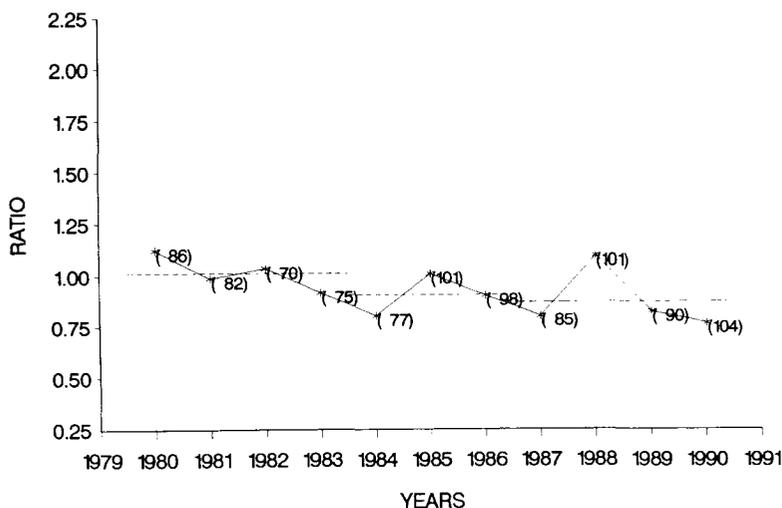


FIGURE 4. Estimated ratios of lung cancer rates for Washoe-Lyon/Clark by year and CFS exposure categories adjusted for age, both sexes, ages 25 to 54.

tory investigators identifying particular immunologic disorders in affected individuals (3), as well as the availability of detailed information from the state wide Nevada Cancer Registry.

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