ORIGINAL ARTICLES

Incidence rates of brain cancer following an outbreak of chronic fatigue syndrome

Cheng-Te Major Lin[1], Naji Younes[1], Paul H. Levine*[2,3]

[1] Milken Institute School of Public Health, The George Washington University, Washington, United States
[2] College of Public Health, University of Nebraska, Omaha, United States
[3] The National Cancer Institute, National Institutes of Health, Maryland, United States

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ABSTRACT

Previous studies utilizing data from the Nevada Cancer Registry suggested a transient increase in non-Hodgkin's lymphoma (NHL) and brain cancer in northern Nevada following an outbreak of Chronic Fatigue Syndrome (CFS) in that area which was not seen in southern Nevada which had no reported CFS outbreaks. A subsequent study from the National Cancer Institute (NCI) using data from the NCI's Surveillance, Epidemiology and End Results (SEER) Program and Medicare documented the association between CFS and NHL on a national basis but no other cancer association was seen. Since brain cancer has a younger age distribution than NHL, we returned to the Nevada Cancer Registry and used ten more years of data and additional analyses to determine if there was an association between CFS and brain cancer by age. This study confirmed the increased incidence of brain cancer following the outbreak in northern Nevada but not southern Nevada with the increase limited to the under 65 age group, thus explaining why the SEER-Medicare analysis only analyzing data in the 65 and above age group did not detect this association.

Key Words: Chronic fatigue syndrome, Brain cancer, Incidence, Nevada

1. INTRODUCTION

Chronic Fatigue Syndrome (CFS) is a common, debilitating disorder[1,2] that has been reported to occur in clusters or outbreaks,[3] initially reported as Epidemic Neuromyasthenia.[4] One such outbreak was reported in Incline Village, NV in 1986[5] and was subsequently studied in more detail by the Centers for Disease Control (CDC)[6] and the National Cancer Institute (NCI).[7] The rationale for the NCI studies was based on the evidence that the three leading candidates for initiating this investigation were considered as oncogenic agents: Epstein-Barr virus (EBV),[8] human herpesvirus-6 (HHV-6)[9] and a retrovirus similar to HTLV-I.[10] Additional impetus for studying the possible relationship to cancer were the concerns of the physicians in Incline Village treating these patients that there was a higher incidence of cancer in their practice than had been previously observed[11] and the observation by Grufferman et al. that an unusual pattern of cancer appeared in the North Carolina symphony in association with an outbreak of CFS.[12,13] Since the Incline Village physicians and Grufferman were particularly concerned about non-Hodgkin's lymphoma and brain cancer, we focused our attention on these two malignancies using data from the Nevada Cancer Registry.[14,15]

In our initial studies, the data supported a transient increased

*Correspondence: Paul H. Levine; Email: paulhlevine@earthlink.net; Address: University of Nebraska Medical Center, Department of Epidemiology 984395 Nebraska Medical Center Omaha, Omaha 68198, United States.

incidence in both NHL and brain cancer in Washoe and Lyon counties (which included Reno) in northern Nevada where the CFS cluster occurred shortly after the peak of the CFS outbreak; no such changes were noted in Clark Country in southern Nevada (including Las Vegas) where no unusual pattern of CFS had been noted. Lung and breast cancer, not suspected of having an infectious etiology, were chosen as control diseases. The association of CFS with NHL was confirmed in a large population-based NCI study involving the Surveillance, Epidemiology and End Results (SEER)-Medicare registry data[16] which analyzed data from 1.2 million cancer cases and 100,000 controls aged 6-99 years, 1992-2005 that was analyzed for all cancers subsequent to the diagnosis of CFS. Only NHL appeared as a statistically significant malignancy linked to CFS. Since brain cancer is known to occur at a younger age than NHL, we decided to use the Nevada Cancer Registry data again with a longer time period and a larger data base to determine if the data continued to support the proposed link between the CFS cluster and brain cancer with particular attention to age at onset of the brain cancer.

2. Materials and methods

The primary brain tumor case data in this study were obtained from the Nevada Cancer Registry. The primary brain tumor data requested included all races, all genders, and ages of 0-19, 20-64, and 65 years and above Nevada residents during 1980-85, 1986-89, 1990-93, and 1994-2000 from Washoe and Lyon counties where had clusters of fatiguing illness, and Clark County where had not affected by the fatiguing syndrome. However, for reasons of confidentiality no data could be released if there were 5 or fewer cases of primary brain tumor during this time in any age group. As a result, we combined the data into two age groups, 0-64 and 65+. We analyzed the data in four groups, considering the period 1980-1985 as the pre-CFS outbreak period since it peaked in 1986 but actually started approximately two years earlier, 1986-1989 as the outbreak period, and the subsequent years as the post-outbreak period, divided into two periods.

Table 1. Primary brain tumor rates in Clark county and Washoe-Lyon counties from 1980 to 2000. *Rates as cases per 100,000 Person-Years

County	Years	Age. Grp	Brain Cancer	Population	Person-Years	Rate
Clark	1980-1985	0-64	128.00	459,541.00	22.98	5.57
Clark	1986-1989	0-64	91.00	575,201.00	17.26	5.27
Clark	1990-1993	0-64	132.00	728,774.00	21.86	6.04
Clark	1994-2000	0-64	299.00	1,029,694.00	61.78	4.84
Clark	1980-1985	65+	55.00	43,478.00	2.17	25.30
Clark	1986-1989	65+	57.00	64,631.00	1.94	29.40
Clark	1990-1993	65+	74.00	86,475.00	2.59	28.52
Clark	1994-2000	65+	189.00	123,745.00	7.42	25.46
Clark	1980-1985	Total	183.00	503,019.00	25.15	7.28
Clark	1986-1989	Total	148.00	639,832.00	19.19	7.71
Clark	1990-1993	Total	206.00	815,249.00	24.46	8.42
Clark	1994-2000	Total	488.00	1,153,439.00	69.21	7.05
Washoe+Lyon	1980-1985	0-64	51.00	200,829.00	10.04	5.08
Washoe+Lyon	1986-1989	0-64	53.00	228,831.00	6.86	7.72
Washoe+Lyon	1990-1993	0-64	47.00	257,028.00	7.71	5.58
Washoe+Lyon	1994-2000	0-64	89.00	304,324.00	18.26	4.87
Washoe+Lyon	1980-1985	65+	15.00	20,596.00	1.03	14.57
Washoe+Lyon	1986-1989	65+	17.00	26,106.00	0.78	21.71
Washoe+Lyon	1990-1993	65+	16.00	30,625.00	0.92	17.41
Washoe+Lyon	1994-2000	65+	44.00	37,000.00	2.22	19.82
Washoe+Lyon	1980-1985	Total	66.00	221,425.00	11.07	5.96
Washoe+Lyon	1986-1989	Total	70.00	254,937.00	7.65	9.15
Washoe+Lyon	1990-1993	Total	63.00	287,653.00	8.63	7.30
Washoe+Lyon	1994-2000	Total	133.00	341,324.00	20.48	6.49

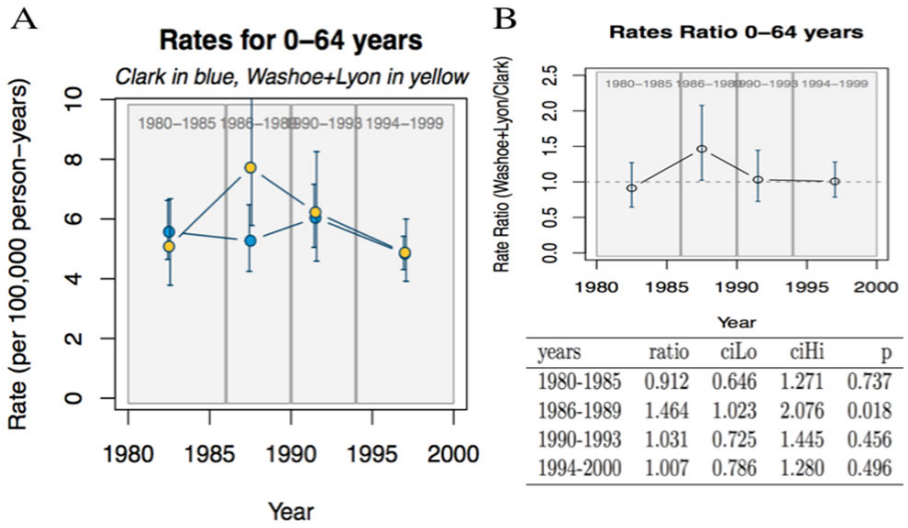
Note. Rates as cases per 100,000 Person-Years

The study compared the primary brain cancer incidence rates in the Washoe/Lyon counties with Clark County. We accounted for population in each age group and period with the estimated population counts, and the duration of the periods, which were 1980-85, 1986-89, 1990-93, and 1994-2000 covered 5, 3, 3, and 6 years respectively to generate meaningful incidence rates. The estimated populations during these four periods were based on the census population counts for Clark, Washoe, and Lyon by age group for 1980, 1990, and 2000, and a quadratic interpolation in each age group and county to estimate the population at intermediate years. The average population over an interval was computed based on the integral $\frac{1}{hi-lo}\int_{lo}^{hi} Pop(x)dx$. The rates were expressed as cases per 100,000 person-years, where the denominator was the average population for the age group and period and multiplied by period duration in years and divided 100,000 (see Table 1). Our study plotted incidence rates and rate ratios for both 0-64 years old and 65 years and above during the four time periods, we could compare the changes in rates in both Washoe/Lyon counties and Clark County. The original data did not include the number of brain cancer cases for 0-19 age group in Washoe/Lyon for 1990-93 due to the data confidentiality. Therefore, we imputed zero to five cases for this particular age group during the period. The sensitivity analyses included 0-5 but the reported results are based on 0, which is the most conservative choice. Rate ratios were calculated as rates in Washoe/Lyon counties divided rates in Clark County. All the figures were presented with the exact 95% Poisson confidence interval bars and one-sided p-value form an exact Poisson test, which tested that the rate ratio was greater than one. We used R version 3.2.2 to analyze the data.

3. Results

In the 20 years of our study, the Nevada Cancer Registry captured 1,025 primary brain cancers in Clark County, 650 of them ages 0-64, and 332 cases from Washoe/Lyon counties, 240 of them ages 0-64 (see Table 1).

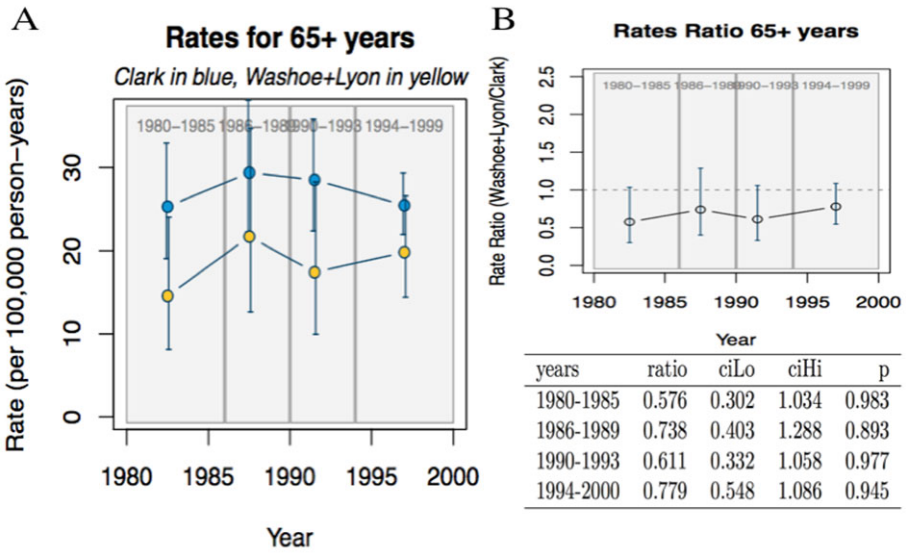
Major differences were seen in the longitudinal pattern in the rates, the biggest difference being in the 0-64 age group which was stable between 1980 and 1989 in Clark County but showed a significant increase in 1986-89 from 5.08/100,000 to 7.72/100,000 in Washoe/Lyon counties following the CFS outbreak. The rates ratio of Washoe-Lyon/Clark, the statistical analysis used in our early description of the cancer pattern in Nevada after the CFS outbreak,[15] was 1.464 (p = .018) 1986-1989. This statistically significant difference described in Table 1 is also portrayed in Figure 1 which depicts both by actual rates and the ratios of the rates in the 0-64 age group.



years	ratio	ciLo	ciHi	p
1980-1985	0.912	0.646	1.271	0.737
1986-1989	1.464	1.023	2.076	0.018
1990-1993	1.031	0.725	1.445	0.456
1994-2000	1.007	0.786	1.280	0.496

Figure 1. Primary brain tumor rates and rates ratio with the five cases imputation in the 0-64 years old population. A) Washoe-Lyon counties (yellow) had significantly higher rates during the outbreak (1986-89) compared with Clark County (blue) where did not have the outbreak when imputing five cases. Quadratic interpolation estimated the population in each county during these four time periods. 95% confidence bars were shown in the graph. B) The ratio Washoe-Lyon/Clark, the exact 95% Poisson confidence interval for the ratio and one-sided p-value from an exact Poisson test, which tested whether the ratio was greater than one. The rates ratio 1.464 (Washoe-Lyon/Clark) was statistically significant (p = .018) during the outbreak period (1986-1989), whereas the pre- and post-outbreak periods had ratios approximately to one were not statistically significant (see table B). Statistical significance is defined as $p < .05$ C.I. 95% two-tailed.

There was no geographic difference in the rates in the 65+ age group (see Figure 2) although there was an interesting increase in the rates from 25.3 to 29.4 in Clark County and a stronger increase from 5.08 to 7.72 in Washoe/Lyon county. There was no difference in the Rates ratios.



years	ratio	ciLo	ciHi	p
1980-1985	0.576	0.302	1.034	0.983
1986-1989	0.738	0.403	1.288	0.893
1990-1993	0.611	0.332	1.058	0.977
1994-2000	0.779	0.548	1.086	0.945

Figure 2. Primary brain tumor rates and rates ratio in the 65 years old and above population. A) Both Washoe-Lyon counties (yellow) and Clark County (blue) had similar rates trends where Clark County was consistently higher than Washoe-Lyon counties throughout the time. Quadratic interpolation estimated the population in each county during these four time periods. 95% confidence bars were shown in the graph. B) The ratio Washoe-Lyon/Clark, the exact 95% Poisson confidence interval for the ratio and one-sided p-value from an exact Poisson test, which tested whether the ratio was greater than one. The rates ratio 0.738 (Washoe-Lyon/Clark) was not statistically significant (p = .893) during the outbreak period (1986-1989), whereas the pre- and post-outbreak rates ratios were also lower than one and not statistically significant (see table B). Statistical significance is defined as $p < .05$ C.I. 95% two-tailed.

4. Discussion

The possible relationship between CFS/ME and cancer has been raised in several reports and reviews[11–15] and is biologically plausible because of the well documented reduction of NK cells in CFS patients[17–21] and even in unaffected family members[17] but the first evidence from a well characterized data base was our report from the Nevada Cancer Registry suggesting an increased incidence of NHL and brain cancer following an outbreak of CFS in northern-Nevada/California.[15] Two aspects of this present report are particularly important: first, CFS/ME is a heterogenous syndrome and post-infectious CFS defined in part by an acute infection and devastating fatigue associated with severe cognitive disorder may have an entirely different pathogenesis and outcome than other forms of CFS. Indeed, our data suggest that recovery at least to some extent appears to be more common in the post-infectious cases of CFS.[22] Second, the evidence that our findings are transferable to a large number of CFS patients is supported by the confirmation a significant increase in NHL following CFS in a comparison of national databases (Medicare and SEER) in the elderly population.[16] The absence of documentation of our observed increase in brain cancer stimulated us to return to the Nevada Cancer Registry which now had ten more years of data and a larger number of control cases (Clark County) as well as brain tumor cases outside of the outbreak period in the CFS outbreak area (Washoe/Lyon counties). The stability of the incidence rates in Clark County, comparable to the stability of brain cancer nationwide according to SEER, support the reliability of its use as a control population for Washoe/Lyon counties in the rate ratio analysis.

The primary limitation in this study is the relatively small population in Nevada which prevented us from analyzing some important factors such as a more precise examination of under 65-age group to see exactly what ages were most affected, which would be of interest since this could be compared to the ages of the CFS population previously reported.[6,7,24] In this study, which involved hundreds of thousands more Nevadans over ten years than the earlier study, we were unable to define the age groups as we originally proposed (0-19, 20-64 and 65+) because the Nevada Cancer Registry would not release numbers in cells less than 5 persons for reasons of confidentiality. Another important

parameter which we could not examine because of the confidentiality issue was the specific tumor types in excess during the transient increase in brain cancer.

In regard to the interpretation of the data, we note the following: The existence of outbreaks of CFS has been well documented, initially described as epidemic neuromyasthenia by Henderson and Shelekov[4] and documented in at least 18 outbreaks.[3] The original Nevada data suggested that the latent period between the development of CFS and cancer is shorter for NHL than brain cancer (the NHL peaked in 1986 and the brain cancer in 1987) but the peak rate ratios were similar. In this study, which involved hundreds of thousands more Nevadans over ten years than the earlier study, the larger control groups with the added time period allow us more confidence in the support that these data give to our earlier study. Another advantage of this study over the previous report is that we were able to analyze incidence data having a population base in addition to repeating the relative case numbers in the CFS vs. control counties. Also of importance is our observation that the increased incidence of brain cancer is solely in the population under 65, and therefore our data are consistent with the SEER-Medicare report of Chang et al. in their larger population-based study.[16]

In addition to decreased NK cell activity being a possible mechanism for susceptibility to cancer in CFS, additional specific risk factors for NHL include immune dysfunction and EBV reactivity, each of them well documented risk factors for NHL.[8, 23–27] The possible mechanism for brain cancer as an outcome of CFS is not readily apparent. Certainly EBV has been shown to cause brain disease[28] and the profound cognitive disorder seen in post-infectious CFS is a clear manifestation of CNS involvement. One possibility is that the agent that triggered the Nevada/California outbreak by itself could be oncogenic and cause brain cancer. HHV-6 has been suggested as being involved in the Nevada/California outbreak[7, 24] and this virus has been reported in brain cancer[23] but an etiologic link of HHV-6 to cancer has thus far not been demonstrated.[29]

In summary, our data strengthen the likelihood that CFS is a risk factor for cancer, particularly NHL and brain cancer. As with a number of other proven associations of oncogenic agents and cancer, this descriptive study will have to be confirmed by analytic studies and/or more persuasive laboratory studies.

Conflicts of Interest Disclosure

The authors declare that they have no competing interests.

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