Nervous system cancer: analyses of historical mortality rates in the United States and Japan indicate sudden increases in environmental risk

by

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ABSTRACT

Nervous System cancer age-specific mortality rates began being recorded for European and Non-European Americans in 1930 and for Japanese in 1952. All ethnic groups show significant historical increases in mortality rates. For the two American data sets, the age-specific pattern for mortality seems to have stabilized starting with the birth cohort of the decade of the 1900s. For the Japanese data set, the pattern stabilizes starting with the birth cohorts of the 1910s and 1920s. These stabilized patterns of NS cancer incidence are similar to the age-specific mortality rates for many other cancers. That is, the rates are higher in the first five years of life then in the next five years, then the rates rise rapidly above the neonatal rate until the age of maturity. During maturity, the rate increases as a constant exponential function and reaches a maximum at around the ages 80-85 years old. Changes in cancer incidence can only be caused by two factors, environmental and genetic effects. Given the suddenness of the change in NS cancer mortality rates, we can rule out the contribution of a possible genetic effect and focus on characterizing a possible environmental risk factor. Herein the possibility of electromagnetic waves from power-grid systems increasing risk for NS cancer is considered, and using the data and historical evidence this possibility is ruled out. In order to understand the relationship between the molecular mechanisms of mutagenesis and the incidence of cancer, a physiologically based quantitative model which includes the processes of mutation, cell proliferation and death. We use the two-stage model of cancer of Armitage and Doll (1957), whereby the first stage is initiation, where “n” events occur to create the first preneoplastic cell which grows slowly at the juvenile rate. The second stage takes place when a preneoplastic cell experiences “m” events which lead to promotion, after which the neoplastic cell will grow rapidly as a tumor. This model has been adjusted by Moolgavkar and Knudson (1981) and Herrero-Jimenez et al. (2000) to take into account cell growth rate and human heterogeneity respectively. This model is applied to the birth cohort of 1920 in order to demonstrate how we can calculate the fraction of the population at primary risk for NS cancer, and how this has changed over time.

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Chapter 1: History of Nervous System Cancer in male and female
European and African Americans and Japanese

For cancers of the nervous system, including eye cancer, there is a trend across the
decades of 1900 to 1980 where incidence is relatively high in infancy, then sharply
declines, then begins to rise at the age of 20 years and continues to do so until there is a
maximum plateau around 80-85 years of age. The overall trend has been an increase in
incidence of NS cancer over the past century, not unlike the trends with many other
cancers of organs, such as lung cancer.

Materials and Methods

Data
Specific cancer mortality data was obtained from MIT’s epidemiology database page
(epidemiology.mit.edu). Dr. Herrero-Jimenez assembled the database and matched the
mortality statistics with population figures. Cancer mortality statistics were first recorded
in 1900 in the US and 1952 in Japan. For NS cancer, mortality statistics were recorded
starting in 1930 in the US. The raw US data is obtained from the Department of Health
and Human Services (1937-1997) and the US Bureau of the Census (1930-1936). Age-
specific population statistics since 1950 were retrieved from the Duke University Center
for Demographic Studies. Japanese data was obtained from the University of Tokyo’s
Department of Public Health. In the analysis of NS cancer, namely brain cancer, the
assumption is made that mortality is a good indicator of incidence, given the lethality of
the disease.

Certain confounding factors include the accuracy of the mortality and population records
compiled by the US government. Another factor is the misdiagnosis of brain cancer.
Cancers of other organs can metastasize into the brain, which might mislead the health
official into incorrectly labeling the disease NS cancer. Conversely, brain tumors rarely
metastasize to other organs. Another confounding variable is the historical changes in
autopsy frequency. Autopsy rates in the US rose during the period of the 1930s to 1960s;
however, since then they have decreased back to the 1930s levels.

Methodology
The data is organized in six different groups: European American males and females, Non-European males and females (of whom 80-90% were of African descent), and Japanese males and females. The number of deaths and population numbers were organized by birth decade cohorts, meanwhile age of death was organized in five year intervals (0-4yrs, 5-9, etc.). The age of death is defined at $t$, and the birth cohorts are defined by $h$. Using these data, we can define the function $OBS(h,t)$, following the method of Herrero-Jimenez et al., as:

$$OBS(h,t) = \frac{\text{observed number dead due to NS cancer of birth cohort } h \text{ and age interval } t}{\text{population of birth cohort } h \text{ live in age interval } t}$$

Herrero-Jimenez have further refined this model to more accurately reflect the risk of getting and dying from a certain cancer. Medical technology has certainly improved over the past century which affects the survival rate given a diagnosis of a certain cancer. For instance, if a certain cancer once was untreatable but is now completely treatable, then deaths caused by this cancer would not be a good measure for incidence. Thus, to the model was added the parameter $SUR(h,t)$, the probability of surviving for five years post diagnosis. For NS cancer, unfortunately we still are unable to cure most cases, and therefore the five-year survival rate is essentially zero. Additionally, the accuracy of diagnoses of certain cancers could also change over time given advances in medical technology. Thus the parameter $REP(h,t)$ was added, which is the probability of an accurate recording derived from the fraction of deaths reported from uninterpretable causes. By 1930, when our US data begins, $REP(h,t)$ was already approximately 1, including the mortality of the extremely aged. Lastly, $OBS(h,t)$ would underestimate the incidence and risk of getting a specific cancer because it does not take into account competing forms of death. That is, a person who has died from one disease would possibly have been at risk for another, had he not died. To address this, the term $TOT(h,t)$ was introduced, which represents the death rate from all possible causes for a birth cohort $h$ and age $t$. Therefore, the adjusted $OBS(h,t)$ is defined as:

$$OBS^*(h,t) = \frac{OBS(h,t)}{(1-SUR(h,t))(REP(h,t)(1-TOT(h,t)+OBS(h,t)))}$$

As mentioned above, $SUR(h,t)$ for NS cancer can be approximated as zero, and $REP(h,t)$ is essentially one. Since NS cancer mortality is a very small portion of total deaths, i.e. $OBS(h,t) \ll TOT(h,t)$, we can approximate the adjusted function as:

$$OBS^*(h,t) = \frac{OBS(h,t)}{(1-TOT(h,t))}.$$

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Figure 1: NS Cancer Age-Specific Mortality Rates in European American Males (1930-1997)
Figure 1 shows OBS($h,t$) for European American Males. The same figures for the remaining data groups can be found in the appendix.

**European American Males and Females**

For European-American males (EAM), for birth cohorts up to the 1860s, there is a significant increase in incidence from the ages of 80 years to 90 years old. From the birth cohorts of the 1870s and onward, there is a steady increase in OBS until slightly before 80 years old when the rate begins to plateau.

Also interesting is the fact that the curves from the cohorts of 1900s onward are almost identical, especially after the juvenile period. The OBS rates seemed to be increasing consistently until the birth cohorts of 1890s and 1900s. For example, a 75 year old born in any decade in the 20th century is about 10 times more likely to die from NS cancer than a person the same age born in the 1860s, only 40 years prior.

In the stabilized cohorts, i.e. 1900s and beyond, the age at which the maximum rate occurs seems to be 80-85.

The data for EAF mirrors those for EAM in shape, but is slightly smaller in magnitude.

**Non-European American Males and Females**

NEAM and NEAF curves follow the same patterns as EAM and EAF, showing a general increase in OBS until the birth cohorts of 1900s and onwards when the incidence stabilizes. While the shapes of the curves are similar to those of EAM and EAF, the magnitude of NEAM is less than EAM and EAF, and the magnitude of the NEAF curves is even lower.

**Japanese Males and Females**

In JM and JF curves, one can see a similar increase in OBS over time, with two interesting differences from the US data. First, the pattern does not stabilize until the birth cohorts of 1910s and 1920s, which is 10-20 years after the curves stabilized for the American cohorts. The second important difference is that the magnitude of the Japanese OBS curves is much smaller than the analogous American curves. These two differences are consistent with observations from other cancer types.
Figure 2: NS Cancer Age-Specific Mortality Rates for European American Males as a Function of Calendar Year of Death

Figure 2 shows the function \( OBS(h,y) \) where \( y = h + t \), for European American males. This allows us to see mortality rates as a function of the calendar year of death. The analogous graphs for the other data groups can be found in the appendix. The advantage of this graph over the plot on the age scale is that it allows us to distinguish those curves which were very similar on the age scale. That is, the birth cohorts of 1900s and onward were almost identical in Figure 1. Here, we can see that these curves do in fact have the same shape and magnitude (i.e. same age-specific mortality rates) but they are shifted according to the calendar year. Whatever the environmental factor was that caused the change in NS cancer incidence for EAM, Figure 2 indicates that it did not occur during or after the lifetime of the 1900s birth cohort. Thus, we can deduce that the environmental factor started taking into effect sometime in the latter half of the 1800s in America for European and Non-European Americans. In Japan, the environmental factor seems to have taken into effect 10-20 years after it did so in the US. Lastly, given that the birth cohorts before stabilization (i.e. before the 1900s cohort for Americans and 1910s/1920s cohort for Japanese) showed no consistency, the environmental factor was probably acting over a long period of time which caused a continual change from the birth cohorts of 1850s to 1900s.

There are other cancers which seem to follow similar, but not identical, patterns. For instance, lung cancer \( OBS(h,t) \) rises with age and reaches a maximum at the age interval of 80-85. There is also a shift due to an environmental factor but the rates stabilize
beginning with the birth cohort of 1890s and 1900s. Another similarity between lung cancer and brain cancer arises when you compare the American and Japanese data. Just as with NS cancer, the environmental factor affecting Japanese lung cancer incidence seems to take into effect 10-20 years later than for America. This may imply that one environmental factor such as smoking cigarettes contributed to the shift in incidence of both lung and brain cancer. Chapter 2 addresses the assessment of a possible environmental risk factor.
Chapter 2: History of the Hypothetical Risk Factor

The figures and analysis in Chapter 1 show that there has been a clear rise in the rate of NS cancer. Most research done recently to discern what environmental factors can increase risk of NS cancer have been case-control studies on a small scale, such as workers in a factory or residents in a town where possible clusters of incidence exist. However, clearly there has been a shift that put a significant portion of the population at higher risk. Acknowledging this leads one to search for a more universal environmental factor to which a significant portion of the population was exposed. Here I demonstrate how to assess a hypothetical risk factor by looking at the appearance of extremely low frequency electromagnetic waves from power lines in American society.

History of American Electric Power Transmission

In 1888 Nikola Tesla introduced the concept of using alternating currents in motors and transformers, paving the way for the development of power line systems. Scientists could now expand upon the already existing electric utility systems and deliver power to homes miles away. In 1907, only 8% of American homes had electricity. By 1932, this figure rose to 67%, however, only 11% of farm dwellings were electrified, compared to well-over 80% for urban settings.\(^3\)

In an attempt to address this concern, the Federal Government passed the Rural Electrification Act in 1936. By 1941, 35% of rural homes were electrified. As technologies improved and demand increased (especially during World War II), so did the amount and breadth of electricity consumption. By 1945, half the farm homes in America were connected to an electric grid, and by 1950, this figure reached 80%.\(^4\)

Health Concerns with Extremely Low Frequency Electromagnetic Waves

Although by the midway point of the past century power lines were ubiquitous in America, concerns about the possible carcinogenic effects of EMFs at extremely low frequency (60 Hz) from these power lines did not rise until a landmark study done in Colorado was published in 1979.\(^5\) The case-control study examined homes which lived close to power lines and had “elevated” levels of exposure to their EMFs. The researchers reported a link between childhood cancer and these elevated exposures. While the strength of the methodology is questioned today, this study’s result, that elevated exposure to EMFs caused increased death in children from all cancers (with odd ratios 2-3), has spurred many more groups to study the health effects of ELF EMFs. The majority of these studies have found no correlation or were inconclusive.\(^6\)

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\(^4\) Ibid.


There have also been several occupational hazard studies which looked at workers exposed to especially strong EMFs. These studies proved equivocal and were too difficult to conduct because of the rarity of brain cancer, small cohort sizes, and crude assessment of exposure levels. One study found a significantly increased risk for glioblastoma multiforme brain cancer.\textsuperscript{7} It should be noted that there is a danger in identifying brain cancer from death certificates since often times tumors of the brain are the result of metastasis from other organs.\textsuperscript{8}

Exposures are typically measured in terms of average magnetic flux density on the order of microTesla. The background exposure level for populations in their homes is less than 0.3\( \mu \)T but those who live near power lines or have increased exposure through their occupation can be exposed to levels above 0.8 \( \mu \)T.\textsuperscript{9}

**Characterization of Environmental Factor**

In light of the speed with which the incidence of NS cancer increased, one can say that inherited genetic factors most likely played a negligible causal role, while some environmental factor caused the change. In characterizing the environmental factor, it is important to determine whether the risk increased gradually over time or very quickly.

The increased exposure to ELF EMFs was most likely a gradual increase. Furthermore, the expansion was staggered when considering the differences between urban and rural populations. In the early 1930s, almost all cities were connected to power grid systems while only 11\% of rural homes were connected, even though the population ratio of urban-to-rural was 56:44. By 1950, power lines were ubiquitous in both settings and the population ratio was 60:40.\textsuperscript{10} Thus, a very significant portion of the population was decades behind another portion of the population in terms of exposure. If we take power line EMFs to be the hypothetical risk factor, then for a little over half the population (i.e. urban) the most significant increase in exposure was between the end of the decade of the 1900s and the early 1930s. For a little less than half the population (i.e. rural), the supposed environmental risk factor should have increased most dramatically during the period of the early 1930s until the early 1950s.

\textsuperscript{7} Ibid.
Conclusions

As mentioned earlier, for EAM and EAF, the mortality due to NS cancer shifted with transition birth cohorts between the 1850s and 1900s. The birth cohorts of the 1900s and onwards have been consistent, but the changes began for birth cohorts decades before. Given this, the environmental factor was most likely introduced well before 1900. In fact, given the changes observed with the birth cohorts, the factor probably started appearing between 1860-1890. Considering the timing of when power-grid systems were established, it is reasonable to rule out the possibility that ELF EMFs from power lines contributed significantly to the shift in NS cancer incidence.

There have been numerous other studies which considered other possible environmental factors. One popular theory is that smoking cigarettes increases the risk of glioma.11 Another possible risk factor includes ionizing radiation.12

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Chapter 3: Physiology and Pathology of Cancer of the Brain

Development of the Central Nervous System

The brain and spinal cord are formed from the neural plate of the early embryo. The NS develops to consist of around $10^{11}$ neurons, each of which forms synapses with $10^3$ other neurons. Placement and connectivity of the neurons, which determine the capabilities of the NS, are determined during embryonic development. In addition to neurons, there are about $10^{12}$ glial cells. There are three kinds of glial cells: astrocytes, oligodendrocytes, and microglia. Astrocytes are the most numerous and serve to protect neurons, induce neurogenesis, regulate synapse formation and synapse transmission and initiate immune responses. Oligodendrocytes synthesize myelin in the CNS and provide growth factors for adjacent neurons.

Unlike the cells of most organs, neurons become postmitotic after embryonic development and have to survive without division throughout the lifespan. Whereas neurons and oligodendrocytes become postmitotic after differentiation, astrocytes seem to maintain the potential to proliferate, as evidenced by the gliotic reaction after lesion. In the brain there are some cells with glial morphology that are now considered neural stem cells. Radial glial cells are one type of neuronal stem cells and are only present during development. In the regions of adult neurogenesis, stem cells are found in the subventricular zone.

Pathology of Glioblastoma and Genetic Risk

Glioblastoma multiforme (GB) is the most common intraparenchymal brain tumor in adults. Unfortunately it is also the deadliest glioma, which are cancers derived from glial-like cells. Gliomas comprise 60 percent of CNS malignancies. Specifically, GB is a kind of astrocytoma, which is a form of glioma. These neoplasts are called astrocytomas because they possess some morphological characteristics of normal astrocytes. As mentioned earlier, systemic metastases are rare. However, the tumors are extremely aggressive in a local fashion, and accordingly GB is nicknamed “whole brain” or “whole CNS” disease. Histologically and morphologically speaking, glioma formation resembles closely normal glial differentiation.

Several genetic abnormalities have been found to be associated with gliomas. They encode for proteins involved in signal transduction, cell growth, cell-cycle control/proliferation, apoptosis, and differentiation and other critical processes. The inactivation of the p53 tumor suppressor gene on chromosome 17p has been found to be

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associated with progression of GB.\textsuperscript{17} Indeed, mutations or deletions\textsuperscript{18} in p53 are found in over 50 percent of cancerous tumors. Alterations in the ARF/MDM2/P53 pathway as well as the INK4/CDK4/RB pathway, which are responsible for cell-cycle machinery, frequently result in gliomas. Additionally, the over-expression of platelet-driven growth factor (PDGF) has been shown to be associated with the progression of gliomas to more malignant tumors.\textsuperscript{19} Amplification of the epidermal growth factor receptor (EGF-R) gene and the expression of angiogenic factors such as vascular endothelial growth factor (VEGF) have been found to be associated with the progression of tumors to GB.\textsuperscript{20} Another growth factor signaling pathway that is frequently altered in gliomas is FGF.\textsuperscript{21} All of these growth factors play important roles in the differentiation process of glial progenitors, further suggesting similarities between glial differentiation and malignancies.\textsuperscript{22}

There are two types of GB. The primary, de novo, form is most commonly found in elderly patients. 80 percent of these cases exhibit an overexpression of EGF-R gene on chromosome 7p. The average age of diagnosis is 55 years. Meanwhile, secondary GB afflicts a younger population with a mean age of 40 years. Inactivation of p53 and overexpression of PDGF ligands and receptors are most commonly associated with the onset of secondary GB.\textsuperscript{23}

\textit{Assessing Historical Environmental Risk Factor}

Considering the development of organs, it is possible to mathematically model the biological processes that ultimately lead to cancer. Armitage and Doll (1954, 1957) modeled cancer as a two-stage process. The first stage is initiation, where “n” events occur to create the first preneoplastic cell which grows slowly at the juvenile rate. The second stage takes place when a preneoplastic cell experiences “m” events which lead to promotion, after which the neoplastic cell will grow rapidly as a tumor.\textsuperscript{24,25}

Chapter 4 consists of the application of the two-stage model in order to analyze the age-specific NS cancer rates in the birth cohorts considered in Chapter 1.

\begin{itemize}
\item\textsuperscript{19} Dunn I.F., et al. Growth factors in glioma angiogenesis: FGFs, PDGFs, EGF, and TGFs. J of Neuro-Oncol 50:121-137 (2000).
\item\textsuperscript{20} \textit{Ibid.}
\item\textsuperscript{21} Markert JM.
\item\textsuperscript{22} \textit{Ibid.}
\item\textsuperscript{23} \textit{Ibid.}
\end{itemize}
Chapter 4: Advanced Analyses

The biological processes by which cancers actually form are not fully understood. It is therefore difficult and illuminating to attempt to mathematically model cancer. As mentioned in Chapter 3, Armitage and Doll (1954) were among the first to do so, modeling cancers as arising from an adult cell population that is constant in number. By 1957, Armitage and Doll proposed the two stage model described in the previous chapter. In 1981, Moolgavkar and Knudson added to the two stage model the terms necessary to account for random division and death of preneoplastic cells.26 Herrero-Jimenez et al. (2000) have added to the model to account for human heterogeneity and demonstrated its application on public records on colon cancer in the US.27 By using their model, we can calculate an estimate for the fraction of the population for a given birth-cohort at primary risk $F$ for dying of NS cancer.

Several parameters need to be defined. As mentioned earlier, “n” represents the number of events required for initiation while “m” represents the number of events required for promotion. Observations of the number and distribution of colonies carrying point mutation in the lungs have lead Gostjeva and Thilly (2005) to argue that point mutagenesis is limited to the fetal-juvenile period and that tumor initiation only happens during this period (up to 17.5 years old on average).28 The cell proliferation rate is defined as $\alpha$ cell divisions per year and the cell death rate is defined as $\beta$ cell deaths per year. Thus the net cell growth rate per year is $\alpha - \beta$. Other parameters include the initiation and promotion rates per year, $c_{init}$ and $c_{prom}$ respectively. In order to account for the deaths by causes connected to primary risk, the parameter $f$ is included as well.

We have applied this model to the birth-cohort of the 1920s to find a best-fit curve to the OBS$(h,t)$ per 100,000 versus age curve. From these fits we can extract a value of $F$. We the range of $F$ at 0.01 to 1.0, meaning we would test values between 1 and 100 percent of the population at primary risk. We set the range of $f$ as 0.05-1.0, because we are unsure how many deaths were caused by something connected to the primary risk factor. The range for $c_{init}$ was set to 0.1-10.0 since this is on the calculated order. We know less about the value of $c_{prom}$ but we know it is rare, thus the range was set to 10e-10 to 10e-6. $\beta$ is set to zero since the cells rarely die. $\alpha$ has a range (and therefore, so does $\alpha - \beta$) of 0.1 to 0.3, which is based on observationally based estimates. We set $n = 2$ and $m = 1$ as a trial. We then have 10 iterations for each of the five parameters done over each one’s range, yielding a total of $10^5$ iterations of fitting curves.

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An example of one of the top ten (i.e. best-fit) of these 100,000 curves is presented in Figure 3 below.

**Figure 3:** OBS(h,t) per 100,000 versus age at death for EAM 1920s birth cohort. The green data set represents the actual data from public records; the yellow data set represents the best-fit curve based on our multiparameter model.

The model curve is based on the following parameter values: $\alpha = 0.122$, $f = 0.78$, $c_{\text{init}} = 7.8$, $c_{\text{prom}} = 7.77e-6$, and $F = 0.01$. If the model were applied to birth-cohorts starting from the 1900s and onward, the fraction at risk would also most likely be the same, indicating that whatever the environmental factor was, it appeared before 1900 and did not change in the past century, which corroborates our ruling out the possibility of power-line EMFs being a factor. Our model assumes that a supposed environmental factor would either increase the number of persons initiated during the fetal-juvenile period, or the number of persons in whom promotion occurs in adult life.

Looking back to Figure 1, we can see that there is no consistency in the curves prior to the birth-cohorts of 1890s and 1900s. It is therefore difficult to pin down when precisely the environmental factor started to play a significant role in NS cancer incidence. Additionally this makes it difficult to deduce whether the environmental factor acts on
the fetal-juvenile period or adult life. Mutation rates derived from the model can serve as an estimate for how many mutations occur, and thus, which genes could be losing their heterozygosity. Further improvement of the model will continue to help elucidate the connections between mutagenesis, cellular kinetics, cancer research and macroepidemiology.
Appendix

EAM Mortality

log-linear EAM Mortality
NEAF Mortality

log-linear NEAF Mortality