A COMPARATIVE ANALYSIS OF AGE-DEPENDENT AND BIRTH YEAR COHORT-SPECIFIC CANCER MORTALITY DATA BETWEEN JAPAN AND THE UNITED STATES

by

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B. S., Environmental Engineering Science (1994)
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Submitted to the Division of Bioengineering and Environmental Health
in Partial Fulfillment of the Requirements
for the Degree of

Master of Science in Toxicology

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Abstract

Using a different approach from previous epidemiological studies, an attempt was made to identify similarities and differences between Japan and the United States via age-dependent and birth year cohort-specific mortality rates calculated for each respective country. Japanese mortality data dating back to 1951 was compiled and entered into a workable format for a set of approximately 50 cancers. The cancers to be studied are limited to lung, colon/rectum, breast, prostate, pancreas, leukemia, Non-Hodgkin's lymphoma, stomach, cervical/ovary, and brain. For this study, the format utilized provides a better means of determining the time periods when environmental factors may have played a role in resulting mortality curves. This new ideology utilizing birth year cohorts as a means of comparing data is more indicative than the past use of age-adjusted mortality rates. Differing experiences of differing birth cohorts in establishing links to mortality trends are the ensuing benefits. With this new approach it will then allow the ability to develop linear relationships with environmental data. As the case is with the American data set, evidence of a linear relationship has been determined between the percentage of smokers for different birth cohorts and the corresponding data for lung cancer. This one example is just a brief introduction to the numerous environmental factors which can be explored in Japan. Such results can then be effectively compared to the United States and other countries to uncover possible ways to prevent different forms of cancer.

Thesis Supervisor: William G. Thilly

Title: Professor of Bioengineering and Environmental Health
Acknowledgments

In every task, there is always others which share the journey when achieving a goal. As my academic career arrives at another step towards my ultimate goal, I too would like to recognize certain individuals which have provided support, either intellectually or emotionally, which have helped me obtain another goal in this crazy setting we call life.

First, I would like to thank my advisor and coach, Professor William G. Thilly, for pushing me in every aspect with this project. Whether providing intriguing views or prompting debate for the good of man, his tenacity will never be forgotten.

Additionally, thanks goes to Dr. Mutsuhiro Nakao and the members of the University of Tokyo’s Department of Public Health for generously compiling the raw data and for Dr. Nakao’s attempts to be of service when others were unable to.

This project could not have arrived to completion without the external thoughts of Pablo Herrero-Jimenez and Janice Vatland. Their guidance and support with the mortality curves is indeed appreciated.

As for my fellow graduate students, thanking them for their patience when answering my questions and listening to my myriad of complaints day in and day out is in order. In particular, much appreciation goes to Brindha Muniappan (my neighbor to the left) for her constant laughter. Aoy Tomita-Mitchell for those sporadic, yet uplifting lunch breaks. Xiaocheng Li-Sucholeiki for being the messenger where Professor Thilly was concerned. Andrea Kim for solid advice and for those coffee runs. And finally, Dr. Per Ekstrom for taking me away from the confines of my computer if just for a few minutes through the discussions of life’s strange mysteries.

Finally, I could not have achieved anything in this life and be happy for it without the support of my family. This one special moment in time is dedicated to them for believing in me and being
there for me whatever the circumstances. Thank you, Mom for your unconditional love and support. Thank you, Monica for your never-ending stories and helping me remember to dream and never lose grasp of it. And thank you, Michael, for helping me never forget the special little details in life.
# Table of Contents

Title Page 1
Abstract 2
Acknowledgment 3
Table of Contents 5
List of Figures 7
List of Tables 8
1. Introduction 9
2. Literature Review 11
   2.1 Presentation of mortality data 11
   2.2 The environment: Japan vs. United States 13
      2.1.1 Japan's introduction to Western change 13
      2.1.2 The changing of Japan's diet 16
      2.1.3 Smoking and lung cancer in both countries 18
3. Materials and Methods 28
   3.1 Materials 28
   3.2 Methods 28
4. Results and Discussion 30
   4.1 Analyses of twelve cancers 30
      4.1.1 Lung cancer 33
      4.1.2 Colon and rectal cancers 35
      4.1.3 Breast cancer 38
      4.1.4 Prostate cancer 39
      4.1.5 Pancreatic cancer 41
      4.1.6 Stomach cancer 42
      4.1.7 Ovarian and cervical cancers 44
      4.1.8 Non-Hodgkin's lymphoma 46
      4.1.9 Leukemia 47
      4.1.10 Brain cancer 50
4.2 Further analysis of lung cancer and smoking

5. Conclusion

6. Suggestions for Further Research

7. References

Appendix A - Age vs. OBS(t) Graphs

Appendix B - Birth Cohort vs. OBS(t) Graphs
List of Figures

Figure 1. Sex-specific, age-adjusted mortality rates due to lung cancer in the United States and Japan, 1955 to 1985.  
Figure 2. Number of cigarettes consumed per adult per year in the United States and Japan, 1920-1985. 
Figure 3: Relative trends in the percentage of smokers by sex and age group in Japan 
Figure 4: Sex-specific, age-adjusted mortality rates for colon cancer in the United States and Japan, 1955 to 1985. 
Figure 5: Relationship between lung cancer mortality and smoking in males in the United States and Japan (1955-1975) 
Figure 6: Relationship between lung cancer mortality and fat consumption in males in the United States and Japan (1950-1975) 
Figure 7a: Age vs. OBS(t) per 100,000 individuals for Lung Cancer (Japanese males) 
Figure 7b: Age vs. OBS(t) per 100,000 individuals for Lung Cancer (Japanese females) 
Figure 8: Birth Cohort vs. OBS(t) per 100,00 individuals for Lung Cancer Age Group 70-74 (Japanese males) 
Figure 9: Percentage of Smokers vs. Subpopulation at Risk for Lung Cancer for EAM and EAF, Birth cohorts 1820-1920 
Figure 10: Birth Cohorts vs. OBS(t) per 100,000 for Lung Cancer (Age group 70-74) for EAM, JM, EAF, and JF
List of Tables

Table 1. Population Rate of Increase in Fastest-Growing Urban Areas 17

Table 2: Sex- and age-specific percentage of smokers aged 20 years and over in Japan 22

Table 3a: Lung Cancer Mortality per 100,000 individuals in Japanese Males per Decade 31

Table 3b: Lung Cancer Mortality per 100,000 individuals for Japanese Females per Decade 31

Table 4: Trend in per Capita Fat Consumption (percentage of calories) in United States and Japan 37
1. INTRODUCTION

Taking historical data and determining trends has been the hallmark of epidemiological research. In this respect, from the observed trends, the focus is then turned to determining what causes are present that could correspond to these changes in data. This is the case with mortality data and environmental effects which many researchers see as the means in determining distinct changes in mortality rates. However, when determining these trends, the methods in formatting this data can produce analyses that does not closely reflect true changes in the rates for mortality. Thus, in this paper, the focus is to present a new format in setting up a mortality database for Japanese mortality from available site-specific cancer data. Results from this format better detail mortality changes of an observed cancer and allow a more accurate interpretation to what years are involved in determining the key period of history that may have placed indelible changes to the mortality data observed.

With this new format, the resulting mortality curves are to be investigated for trends which will then be compared to that of the American data set. But what observations are to be targeted? In essence, the distinct differences between the two nations will dictate the focus of the observed death rates. One such difference is the advent of industrial change. In the United States, the invention of the cotton gin by Eli Whitney in 1793 was the beginning of the Industrial Revolution. This period starting in the early 19th century, undoubtedly altered the economic and social changes of the most prosperous nation in the world. However, the arrival of these changes were not evident in Japan until the early 20th century when the repercussions of the Meiji Restoration ensued. In 1868, the birth of sweeping changes to Japan’s isolated habitat began with the West bringing new items of innovation. Heretofore, one focus of this paper is the approximately 30 year period difference in the revelation of a newer, faster society in both countries. Examining the tell-tale signs of progress of both countries plus the analyses of Japanese data to that of American data will help establish if industrial-based trends may be present and provide proof of how such similar revolutions affect cancer mortality. Additionally, a historical look into the changing diet of the Japanese is of much interest since their traditional diet is of great distinction to that of the American diet. And with the emphasis placed on fat
consumption in both countries, addressing this issue and coinciding it with the data can help illustrate if a relationship should be pursued. Moreover, in the keen interest of smoking's effects on lung cancer, a narrower focus on the arrival of manufactured cigarettes in Japan after use in the United States will be investigated to determine how similar environments do indeed dictate the observed mortality rates in both nations. Since the new format is age-dependent, indications to corresponding periods of changing history is meant to effectively pinpoint a time table to correlate with environmental change. Consequently, further steps in research can then be based on these strong historical trends found in the mortality data.
2. LITERATURE REVIEW

2.1 Presentation of mortality data

Interpreting data relies on effectively formatting the data to provide a picture of what trends are occurring. This has been the means for nearly a century in the case of mortality data. However, in the past, the method that such data has been analyzed conveyed trends by calendar year with no regard to the differing age groups by birth year within that calendar year. Therefore, with this study, it was of great interest to analyze the Japanese mortality data with respect to age group and their corresponding birth cohorts. Before showing the differences with what interpretations can be seen with this form of data, it is best to provide a background to how mortality data has been previously investigated.

With the case of mortality data, the basic formulas are straightforward and logical, but the attempts are limited with respect to deaths relative to age groups historically. To give an idea to the reasoning behind what has been used in the past, a quick summary of crude death rate, age-sex-specific death rate, and age-adjusted death rate will be described.

A crude death rate is the most basic of terms. In this case, it is a ratio of the number of deaths (from a site-specific cancer) to the total population at mid-year (Zopf, 1992). It is therefore expressed as such:

\[
\frac{\text{Deaths in a given year}}{\text{Total population at mid-year}} \times 1000
\]

Multiplying the ratio by 1000 thus gives a rate per 1,000 individuals. Therefore, if 500 individuals died in 1990 from a total population of 100,000, then the crude death rate would be 5 deaths per 1,000 in 1990. As the term suggests, this estimate does not take age into account. Thus, refining this equation with respect to age leads to the term age-sex-specific death rate.
This calculation refers to the death rate for a certain age group. In other words, where a crude death rate is general with no regard to age, the age-sex-specific death rate is a ratio of the death of an age group, specific for sex, in one year to the number of individuals of that group alive at mid-year (Zopf, 1992). Therefore, the resulting equation gives:

\[
\frac{\text{Deaths of an age-sex-specific group}}{\text{Total number of individuals of that group at mid-year}} \times 100,000
\]

In this respect, the resulting calculation is more detailed where the death rate is sex-specific (i.e. male or female) and more importantly, age-specific, as well. This provides a more detailed death rate which denotes a given year. To exemplify this determination, taking an age group of Japanese males from 20-24, if the number of deaths is 5,000 in 1990 and the number of individuals in this age group numbers at 2,000,000, the age-sex-specific death rate is then 250 per 100,000 individuals. But to compare these rates for different calendar years, the age-adjusted death rate is then utilized.

Where the age-sex-specific death rate narrowed the focus to a certain age group, the age-adjusted death rate goes a step further and provides a calculated death rate in an actual population given the same age distribution of a standard population. In essence, this calculated death rate is a "direct method of standardization" (Zopf, 1992). The end result thus gives the opportunity to compare different populations (i.e. different calendar years) for which age-specific death rates are available. As the case with every study, the basis for comparison is then dictated on the standard population chosen. Therefore, with a given age-sex-specific death rate, using the example 250 per 100,000, and a standard population of 2,220,000 chosen from 1940, one determines the number of deaths for the year in question (e.g. 1990), where the number of expected deaths for that year to be 5,550. If done for each age group in that given year, taking the expected total deaths and dividing by the total standard population in 1940, one then calculates the age-adjusted death rate for 1990. As recognized by this procedure, this death rate is determined via a standard population which is used as a basis for comparison of different calendar years. This leads to the reasoning why such calculations, as forthright as they are, reflect only relative changes in mortality via a baseline population. This method is consistently being used in practically every
cancer epidemiology study, and it's attempts for denoting trends relies on these age-adjusted death rates for the available data. A prime example of this is it's use by Wynder et al. in the studies involving Japanese data (1991, 1992). As seen in figure 1, the age-adjusted mortality rate for lung cancer is seen for calendar years dating back to 1955. Such a study is just the tip of the iceberg of what one can find with the mode of presenting national mortality data.

2.2 The environment: Japan vs. United States

2.2.1 Japan’s introduction to Western change

Although the United States and Japan are now deemed world powers, the differences that encompass these nations are more of practical means. As usually the case with nations from the West to those of the East, the cultural differences seem to have dictated how inhabitants in both nations live their lives. This is certainly the case here where the advance of technology in the United States superseded that of Japan, and thus a lag in development was seen in the latter. This difference in human advancement, illustrated by the mortality statistics, may be a factor in drawing a historical picture by these numbers. Therefore, a brief synopsis of the differences in the environment, both industrial and cultural, is necessary to set the stage in elucidating and examining possible reasons for the contrasting mortality rates in both nations.

Located east of the Korean peninsula and mainland China, Japan has endured thousands of years of isolation. However, in 1543, this changed when Portuguese sailors who where blown off course, landed on Japanese ground by accident (Sims, 1973). After this initial exposure, the Japanese people felt a sense of insecurity with the arrival of strangers to their peaceful existence. But this was all to change in July, 1853, when Commodore Matthew C. Perry of the United States landed in Japan and persuaded the Japanese into signing treaties which commenced open trade between the two nations. Although it was in the interest of the Japanese to stay secluded spurred by the isolationist policy of the Tokugawa rulers, the fear of dangerous repercussions
Figure 1: Sex-specific, age-adjusted mortality rates due to lung cancer in the United States and Japan, 1955-1985

(Wynder et al., 1991)
from ignoring the West were of much concern (Andrews, 1971). This was the beginning of troubles for Japan where the new visitors demanded situations with no regard to Japan’s traditions or wants. Nevertheless, treaties were signed and the West eliminated Japan’s isolation from the rest of the world. But this event embarked Japan on a journey which saw the gradual disappearance of steadfast tradition in exchange for new technology and social advancement.

Ironically, with the arrival of the West, there came major conflicts within the nation that saw a samurai revolution, a coup d’etat that restored power to the Emperor (Meiji), and a civil war. Nevertheless, after all these struggles of power, a government was established with samurai reformers dictating action; a government “governed by samurai firmly dedicated to modernization” (Sims, 1973). This era of modernization, 1868-1912, is now known as the Meiji Restoration.

Comparing the history to that of the United States helps establish differing social environments that developed from the technological gap between these two nations. As evident by the historical background, Japan’s introduction to Western ideas sparked a new means of living. The incorporation of power machinery and the introduction of new items, especially beef, delivered Japan from a country of rice and pickled vegetables to one of assimilating to Western culture. However, before such events occurred in Japan, the United States had already begun it’s phase into advanced technology. The “Industrial Revolution” which began in the late 18th and early 19th century was seeing it’s effects by the mid to late part of the 19th century. With the increasing number of innovations came luxuries that developing nations could not even fathom.

Interestingly, when examining this “technology transfer”, it is important to note how quickly this reformation of one society developed. To begin, Japan’s need for change was sparked by the government as a whole, thus steps in this direction were taken with the help of increasing yields of production of its agriculture, most notably, rice (Dempster, 1967). As such, between 1880 and 1920, rice yields rose 80% in this period, which in turn produced profits for the government to improve the industrial aspect of the restoration. However, there was a drawback to this situation. Products were not in demand considering more than 80% of the population were farmers and
since being heavily taxed, had a very small purchasing power (Andrews, 1971). As a result, it is accurate to assume that even with this rapid, widespread adoption of industrial change, the effects were not seen nationwide, until the early 20th century. This can be noted by the increase in population of urban areas in Japan. Yazaki presents these facts in a table where the rate of increase is seen in the larger cities from 1878 to 1897 (see table 1) (1968). A redistribution of residents was also seen in the latter half of the Meiji period where the five largest cities had a rate of increase in population of 40% in 1910 (Andrews, 1971). With urban cities seeing the first wave of change, the citizens in these areas were more likely to be exposed to the Western culture than rural areas. Thus, movement was essential for adoption of these changes, and with the migration being evident in the latter period of the Meiji Restoration, the effects of these changes were seen at approximately 1920.

2.1.2 The changing of Japan’s diet

Concomitantly, experiencing the pleasures of Western culture was also more visible in the urban areas of Japan. By the early 20th century, the ex-samurai, who helped pull Japan into a more technically advanced nation, were being assimilated into the ways of Western man through changes in the home, clothes, and diet (Yazaki, 1968). Although there was still tradition in the home, the changes undoubtedly altered the ways that Japanese normally lived. As the case with meat, it was not until 1872, that the emperor was persuaded to eat beef for the first time (Sims, 1973). After which, meat-eating and milk-eating were promoted by the government. But as mentioned before, until Japan was firmly situated into it’s restoration, such luxuries were not bought by the common citizen prior to the early 1900’s. Moreover, the true adoption of Western cuisine was not felt until after World War II. Beginning with the rebuilding of the nation after the war, the introduction of wheat and the push for imports began a new social-changing Japan.
Table 1: Population Rate of Increase in Fastest-Growing Urban Areas

<table>
<thead>
<tr>
<th>City</th>
<th>Population in 1897</th>
<th>Rate of Increase, 1878-1897 (1878 population = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tokyo</td>
<td>1,330,000</td>
<td>188.60</td>
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<tr>
<td>Osaka</td>
<td>750,000</td>
<td>258.39</td>
</tr>
<tr>
<td>Kyoto</td>
<td>320,000</td>
<td>142.84</td>
</tr>
<tr>
<td>Nagoya</td>
<td>250,000</td>
<td>222.52</td>
</tr>
<tr>
<td>Kobe</td>
<td>190,000</td>
<td>1,628.98</td>
</tr>
<tr>
<td>Yokohama</td>
<td>180,000</td>
<td>306.57</td>
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<tr>
<td>Hiroshima</td>
<td>110,000</td>
<td>148.52</td>
</tr>
</tbody>
</table>

(Yazaki, 1968, pg. 312)
What many studies pursue in their aim to connect environmental factors to mortality deaths is the issue of diet (Roebuck, 1992; Rose and Connolly, 1992; Wynder, 1992). However, keeping with the historical perspective to Japan’s experience entails the gradual increase in fat products during the latter of the 20th century. As stated before, rebuilding after World War II was the biggest effort by the Japanese government. With help from the Korean War, the economy began to flourish, and the ability to increase the availability of more Western products was more prominent (Longworth, 1983). What is amazing about this period was the transition being more evident in the country’s society. Since relying on wheaten-based products, and luxuries (meat, eggs, dairy products) becoming more common, a revolution began that provides a time-table for investigators when analyzing incidence and mortality data. Thus, it is imperative to consider that the changes that took place in Japan were at the middle of the 20th century, when Western cuisine was beginning it’s infiltration into the traditional diet of previous centuries.

Consequently, studies have used the diet change in Japanese to account for the increase in certain cases of cancer, most notably that of colon and breast cancer (Hara et. al., 1985; Kato et. al., 1987; Miller et. al., 1978; Weisburger, 1997; Lubin et al., 1986; Wynder et. al., 1992). A study by Kato calculated correlation coefficients between foods/nutrient intakes and age-adjusted mortality rates and concluded that fat intake was significant in causing breast and ovarian cancer (1987). Taking the idea that fat intake has increased 3.6 times from 1949-1984, such a strong correlation may indeed explain the increasing trend in breast cancer patients in Japan. This is just one example which provides evidence to suggest that changes in the diet of Japanese may show responsibility to the changes in cancer mortality for certain cancers.

2.2.3 Smoking and lung cancer in both countries

In 1912, the first strong connection made between cigarette smoking and lung cancer was made by Dr. I. Adler. Although this was published early in the 20th century, not until the middle of the century did the insurmountable steps to curtail the use of cigarettes begin. With it’s discovery by Columbus in 1492, the presence of tobacco in nearly every culture in the world has been a steady
but overpowering infiltration that now has been a matter of concern for both health professionals and the average person. In this section, the trends seen in smoking habits for both the United States and Japan will be discussed plus what the literature reports on the ensuing effect of lung cancer.

Some reports give different times to the beginning of smoking prevalence in both the United States and Japan. Although tobacco was a common item in both countries, the advent of the cigarette into mass production can essentially be called the catalyst to this growing market. In the United States, "cigarette girls" rolled up cigarettes for customers until the late 1870's when the invention of the Bonsack machine redefined a new era that yielded tobacco products for widespread use. Epidemiologically, the years in which Americans, both males and females, began smoking is roughly before 1880 and around 1910, respectively (Harris, 1983). However, another study uses the consumption of cigarettes by both nations and concludes that Americans began smoking 20-30 years before the Japanese began between 1940 and 1950 (see Figure 2) (Wynder et al., 1991). Coincidentally, this was at the time of World War II, when rationing of cigarettes were at its highest in Japan, and the availability of cigarettes did not rise until several years after the war ended. But historically, the demand for cigarettes was indeed high before the 20th century in Japan; however, the supply was not there (Okurasho, 1905). In a report that describes the tobacco monopoly in Japan around the turn of the century, it states that an insufficient amount of product could be manufactured for the great demand at the time. Thus, the Tobacco Monopoly Law, promulgated on April 1, 1904, changed the means of tobacco production. Before such action was taken by the Japanese government, the small scale manufacturers did not produce the high quantity seen after 1900. With the government in control, an improvement in manufacturing, an increase in the importation of tobacco leaves, and the fixing of price, there ensued a vaulting of production of cigarettes in Japan (Okurasho, 1905). As a result, while other studies suggest differing times to the beginning of significant cigarette smoking in Japan, history shows that with government control in 1904, the high demand is alleviated through improved technology and an increase of smokers naturally ensued. Nevertheless, the consumption of cigarettes by both nations differ drastically.
Figure 2: Number of cigarettes consumed per adult per year in the United States and Japan, 1920-1985.

(Wynder et al., 1991)
Manufactured cigarettes consumed by males and females ages 15 years and older were 20,954 in 1920 for Japan and 44,656 for the same year in the United States. By 1950, the numbers both increased to 65,298 and 360,199 for Japan and the United States, respectively (Nicolaides-Bouman et al., 1993). Indeed, the number of cigarettes consumed increased to amazing numbers (most notably in the United States), but another important statistic documented is the percentage of smokers in both nations. Tominaga gave evidence of such numbers where sex- and age-specific percentage of smokers aged 20 and older in Japan were given (see Table 2) (1986). As indicated by the table, there has been a decrease in the number of males smoking where a high of 82% is seen in 1967 and in 1984, the percentage drops to 65.5. In the case of females, however, there seems to be a consistency in smoking habits, where the percentage has been maintained at 15. It should be noted that obtaining data on smoking habits for Japan was not gathered until 1958 by Japan Tobacco Inc., the premier supplier of tobacco products in Japan. And as the case is with Japan, such percentages are also available for the United States, where male smokers comprised 50% of the population in 1955, and females, 27%. However, where the percentage of males seem to be decreasing with a low of 31 in 1985, females reach a maximum of 37% in 1979, and gradually decrease to 28% in 1985. With numerous reports indubitably showing a connection between smoking and lung cancer, such discussion of these cases is warranted to provide what scientists have analyzed to show just cause. However, this look into the studies will be focused on what has been seen with lung cancer in the United States and Japan. Since lung cancer is shown to have increased dramatically in the past century globally, it is now said that 80 to 90% of all cases are caused by tobacco, mainly the smoking of manufactured cigarettes. To coincide this statistic, lung cancer was the leading cause of cancer death in men for 28 countries back in 1986 (Cullen, 1986). This being the case, enormous strides to control this worldwide epidemic have been numerous, and as indicated by the smoking statistics shown earlier, the effects of such efforts may actually be materializing.

Using these statistics, comparisons can be made between countries to identify if smoking is indeed responsible for what is being experienced by said countries. This is indeed the case with Japan and the United States, where several reports have provided mortality data for lung cancer
Table 2: Sex- and age-specific percentage of smokers aged 20 years and over in Japan

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(Tominaga, 1986)
and shown how smoking interacts with this data (Krisstein, 1986; Wynder et. al., 1986, Tominaga, 1986, Wynder et. al., 1992). Tominaga, in a presentation to the International Agency for Research on Cancer, conveyed cancer patterns related to smoking. His main focus was incidentally on lung cancer, but he did provide information on the trends of age-adjusted death rates for numerous cancers, including stomach, colon and rectum, breast, and pancreas. The most insightful information deals with the trends of the percentage of smokers per age group for males and females. In a graphical format, he identifies that although females maintain similar smoking habits for the period 1967-1984, there seems to be an increase in female smokers for the age group 20-29, which indicates a strong tobacco following by the young Japanese woman of today (see Figure 3).

When comparing Japanese data to American data, there seems to be a consensus that there are similar trends between both nations. Krisstein reports that barring major changes in policy, he expects an epidemic of lung cancer in underdeveloped countries over the next 20 to 40 years (Krisstein, 1986). Using Japan as an example and using a 20-year lag time for the effects of smoking, he shows a similar relationship between the United States and Japan. Using the following equation:

\[ Y_i = a + bX_{i-20} \]

the relationship between mortality rates and per capita cigarette consumption results in a calculated slope of 0.0061 for Japan, which is very close to the United States’ value of 0.0076. In conclusion, Krisstein states that the mortality rates for Japan will be rising as seen in the United States and that Japan, being representative of a non-Western developing country, is indicative of what such countries are to expect. Although simplistic in it’s statistical method, other studies have concluded similarly. Wynder et. al.’s study on the comparative epidemiology of cancer between the United States and Japan give thorough analyses of the effects of smoking, alcohol, and diet to the differences in cancer trends. Reporting similar data to that of Tominaga for Japan, this study includes US data as well. Graphical representations of sex-specific, age-adjusted mortality rates versus calendar years was done for each cancer (see figure 4).
Figure 3: Relative trends in the percentage of smokers by sex and age group in Japan

(Tominaga, 1986)
Figure 4: Sex-specific, age-adjusted mortality rates for colon cancer in the United States and Japan, 1955 to 1985.

(Wynder et al., 1991)
these graphs for comparison between Japan and the United States, this study concludes that the differences in social habits could be responsible for “substantial differences in mortality rates of specific anatomic sites” (Wynder et. al., 1986). Moreover, Wynder et. al., several years later revisited this topic and expanded on their conclusions by stating that fat intake shows a linear relationship to lung cancer, and that this dietary fat “may modulate the carcinogenic effects of tobacco smoke” (Wynder et. al., 1992). This was concluded from the analyses of comparing smoking and fat intakes in the years 1955 through 1975 to age-adjusted mortality rates recorded 10 years and 20 years later as seen in figures 5 and 6.
Figure 5: Relationship between lung cancer mortality and smoking in males in the United States and Japan (1955-1975)

(Wynder et al., 1992)

Figure 6: Relationship between lung cancer mortality and fat consumption in males in the United States and Japan (1950-1975)

(Wynder et al., 1992)
3. MATERIALS AND METHODS

3.1 Materials

In order to model Japanese data alongside American data, the means in which it was formatted is very important. Herrero-Jimenez et al. developed a format for American data in which the mortality deaths were entered for each calendar year for each five-year age group beginning with ages 0-4 and extending to the age group of 100 and over (1998). The raw data from the Ministry of Health and Welfare was generously copied by Dr. Mutsuhiro Nakao from the University of Tokyo. The raw data was provided in a format similar to that of American data from the United States Department of Health, Education, and Welfare. In addition, total population numbers were entered for each calendar year dating back to 1951, the first year Japanese data is well-documented. This format, done in Microsoft Excel, then calculated the mortality rate of observed deaths (OBS(t)) per 100,000 inhabitants. The purpose of this procedure was to give a weighted value to the observed deaths and then provide a means to compare these values with each birth year for each age group as previously mentioned before.

3.2 Methods

Use of excel format to establish continuity of data

The format seen for the United States data was utilized in compiling the Japanese data. As such, the comparative analysis can be accomplished with great consistency. The only drawback is the differing periods of available data where certain cancers in the United States date back earlier than 1951. The entering of data was performed for all cancers provided. Using the American data as a guideline, the Japanese data was entered and reviewed to confirm consistency with changes in the International Classification of Diseases. Since the data spans four decades, there were four changes in these classifications, and it was necessary to observe these changes to avert any incorrect allocations of mortality values. To complement an accurate depiction of a compare
and contrast mode between both nations, the twelve most prevalent cancers seen in the United States were then analyzed. The list of these twelve cancers are identified below:

1. Lung  
2. Colon/Rectum  
3. Breast  
4. Prostate  
5. Pancreas  
6. Stomach  
7. Cervix uteri/Ovary  
8. Non-Hodgkin’s lymphoma  
9. Leukemia  
10. Brain
4. RESULTS AND DISCUSSION

4.1 Comparative analyses of twelve cancers

The main aspect of this project focused on the analyses of the data through a different mode of graphical format. In establishing what initial results showed, an example of these results for lung cancer is shown in Table 3a and 3b and figure 7a and 7b, where the OBS(t) per 100,000 are grouped in birth-year decades and graphed to show its trend by age. Additionally, the mortality graphs for each cancer are located in Appendix A for easy reference. In effect, each cancer provided an overall depiction of what different birth cohort decades dating back to 1850 experienced for all age groups. Therefore, as the case with lung cancer, there is an indication of a sharp increase from birth cohort decade 1860 to 1870 and subsequent jumps in mortality which suggests that individuals in these birth cohorts may have experienced different environments to those of earlier birth cohorts (i.e. 1840’s and 1850’s). With every cancer, a direct comparison was made between the United States and Japan.

The primary analysis done converted the data into a graphical presentation showing birth cohorts against observed deaths for several age groups. This setup identified the trends and provided a means to clearly compare the differences between the United States and Japan. Moreover, this format at analyzing data is very different to the approach that Wynder explored when examining trends for certain cancers in his study (1986). His approach concentrated on sex-specific, age-adjusted mortality rates where data for all age groups for each cancer was examined for each calendar year. As mentioned before, this examination does provide information on the deaths for each calendar year, yet fails to compare different groups of people born in the same year falling victim to a specific cancer. As a result, there is no direct relationship given to how people experiencing the same environment can be compared to other birth cohorts and thus convey changes in the environment as responsible to identified trends. Therefore, this means of analysis was chosen in the given format to better analyze the data in discovering a person’s environment as the cause for trends seen in mortality data rather than making generalizations like previous studies.
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Figure 7a: Age vs. OBS(t) per 100,000 individuals for Lung Cancer (Japanese males)

Figure 7b: Age vs. OBS(t) per 100,000 individuals for Lung Cancer (Japanese females)
on data using a standard population to dictate comparability. What ensued in most cases were significant differences with respect to the most prevalent cancers seen in the United States. For each cancer, the analysis of converting the data into a graphical presentation showing birth cohorts against observed deaths for several age groups is exemplified in Figure 8. In each case, with respect to the age group, one can identify an increasing or decreasing trend plus determine the year at which this slope change occurred. What is interesting about this form of analysis is the simplicity in identifying sharp contrasts between both countries. The graphs for each cancer, male and female, and their respective age groups can be found in appendix B; however, an overview of what was ascertained is discussed to some extent.

4.1.1 Lung cancer

To begin, an initial analysis was done on lung cancer which identified a striking similarity between European American Males (EAM) and Japanese Males (JM) where a steep increase is observed in the number of deaths for the older age groups (60-64 and 70-74). If one views the graphs, one discovers that the increase in slope for JM is almost exactly to that of EAM. In response, this clearly suggests the effect of cigarettes on the mortality rates in Japan as the case is undoubtedly seen in the United States. As for the female population, Herrero-Jimenez, in his analysis of the effects of smoking on EAM and European American Females (EAF) identified a 30 year lag between the first glimpses of an increase in lung cancer mortality for EAM and EAF (Herrero-Jimenez, personal communication). However, when one considers toying with this idea for JM and Japanese females (JF), such a lag is not evident. What is evident is a slow, but gradual increase in the number of deaths compared to that of EAF. This situation, however, will be further analyzed more thoroughly with a comparative example seen with American data. In the other cancers, a general approach to the findings will be discussed. Each cancer will be touched upon for any significant trends and the relationship will then be analyzed coinciding with the history of given causes to each disease and the status of the United States and Japan with such variables in mind. As a result, the findings should help validate time periods where
Figure 8: Birth Cohort vs. OBS(t) per 100,000 individuals for Lung Cancer Age Group 70-74 (Japanese males)
environmental factors can be linked to mortality rates seen for each cancer. Moreover, this identification of trends will illustrate the advantage of age-dependent birth year cohort-specific data over the previous use of age-adjusted death rates.

4.1.2 Colon and rectal cancers

In the case of colon cancer, it was in the best interest of what is currently known about this disease to include rectal cancer in this comparative analysis. Although they are analyzed together, the results were identified in individual formats. When colon cancer is discussed, the one cause which has consistently been noted is the factor of dietary fat in the average American. The effect of its oxidized product, the elevated production of free bile acids, and the production of fecal mutagens and ketosteroids have prompted such a strong impression to its relevance (Creath, 1990). As the colon graphs show for all designated age groups, there is a constant mortality rate of 100 per 100,000 Americans for both males and females. However, the mortality rate for Japanese males and females have a steeper increase where males born in 1879 die at a rate of 20 per 100,000 and those born in 1922 are dying at a higher rate of 60, which is approximately two-thirds of what it is in the United States. Therefore, a Japanese in 1951 compared to one in 1994 did not share a similar background suggesting a possible environmental factor involved.

And as the case in the United States, the idea of dietary fat being responsible for this increase is being transferred to the Japanese. The “westernization” of Japan has been singled out as the cause to the observed evolving changes, and the increase in colon cancer is just one of them. Ikuko et. al. showed in their study that data spanning from 1949-1984 of Japanese residents gave relative risks for colon cancer due to fat intake at 2.67 for men and 2.30 for women. One might conclude such an increased risk to be confirmed by the increase in the disease historically. However, as mentioned before, the increase in fat consumption did not begin until after World War II, and moreover, this increase does not reach half of American intake numbers until the 1990’s. A study denotes this increase in fat consumption with evidence exemplified by Table 4 (Wynder et al., 1992). As the data shows in each age group, the later the birth cohort, an increase
in mortality ensues. Unfortunately, more studies need to be done to confirm fat consumption as the sole contributor. Although the data shows an experience change in diet after the 1950’s, other environmental factors cannot be ruled out.

Coincidentally, rectal cancer has been a constant partner to the effects taken upon colon cancer, where it is assumed that what affects the colon will normally affect the rectum due to its location. However, the data suggests that there may not be a connection with the differing mortality trends in both nations. As colon cancer indicates a steady-state of deaths in the United States, there is a noticeable decrease in rectal cancer in later birth cohorts. And what is more intriguing is the mortality rates seen in Japan. Where colon cancer seems to be on the rise, the number of rectal cancer deaths seems to be either steady or declining. Furthermore, the number of rectal cancer deaths in Japan is seen to be higher than that of Americans, both male and female for birth cohorts after 1910 for early age groups and for birth cohorts after 1890 for later age groups. Amazingly, the effects are sporadic in terms of different birth cohorts for changing trends in all age groups. It is evident from these graphs that no one environmental factor can be responsible for the changing trends.

And what do studies suggest as causes to rectal cancer in Japan? Several studies have denoted alcohol, namely beer, as an increasing factor (Kabat et. al. 1986, Kune et. al. 1987, Ribol et. al. 1991). Yet, other studies showed this to be untrue (Potter and McMichael 1986, Tuyns et. al. 1988). Another study actually listed numerous foods and examined the relative risks with respect to the number of Japanese that ate these items and were later diagnosed with rectal cancer. The results showed an increased risk with salty foods, boiled fish, and pickled vegetables (Hoshiyama, 1993). What mostly results from what is seen in the data and the literature is that there is inconclusive results to the differing trends seen between colon and rectal cancer, and that epidemiologically, the diet question provides no firm conclusions to explain these trends.
Table 4: Trend in per Capita Fat Consumption (percentage of calories) in United States and Japan

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<tr>
<th>Year</th>
<th>United States</th>
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<tr>
<td>1950</td>
<td>40.0</td>
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<td>1955</td>
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<td>1985</td>
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(Wynder et al., 1992)
4.1.3 Breast cancer

Breast cancer is the leading form of death in American women thus research for this type of cancer is at an all-time high. Nonetheless, there has still been few earth-shattering breakthroughs to the etiology of this disease. It has been postulated that a high-fat diet is one reason for the high incidence of breast cancer in EAF. Additionally, the discovery of the \textit{BRCA1} gene is said to be the genetic basis for familial breast cancer in society, although only placed at 5-10% of all cases (Watanabe, 1993). Interestingly enough, viewing the mortality data for both the United States and Japan helps illustrate such ideas and provides a physical picture in trying to validate them.

When one investigates the trends seen in both American and Japanese data, one would be surprised to see a constant number of deaths in all age groups for EAF and a slight increase in deaths for JF. What is evident about this data is the increasingly high number of deaths in EAF compared to that of JF. EAF show the highest number of deaths at 100 per 100,000 females at ages 70–74, whereas JF show an increase which results at 20 deaths per 100,000 Japanese females. Such evidence show that no change has occurred in the past 100 years for American females that indicate any trend (increase or decrease). However, with the JF, the increase seen in all age groups should be explored.

With the discovery of the \textit{BRCA1} gene, evidence to connect the genetic variable should provide better answers to its involvement in causing of breast cancer. Unfortunately, as stated earlier, the percentage of cases, approximately 5-10%, are deemed familial regarding this gene. And such numbers are seen in Japan as well, thus genetics cannot entirely explain the difference in deaths between both countries (Watanabe 1993, Inoue et. al. 1995). Additionally, a study by Stanford et al. showed that the migration of Asian women, both Japanese and Chinese, to the United States prompted an increase in breast cancer incidence relative to women in the Asian countries (1995). This identifies that environmental factors must be the reason for the differences seen between the United States and Japan. This returns to the idea of fat consumption being a key factor to the higher mortality seen in American females to that of Japanese. However, one event which has been another cause of debate is the dropping of atomic bombs on Hiroshima and Nagasaki. What
is interesting about this event is that reports show an increase of deaths, but not a significant
trend that would explain the national increase seen in Japan. Moreover, these same reports
indicate that the candidates for breast cancer who were exposed to radiation are women under 20,
thus suggesting women born around the mid-1920's. The time frame to when these women
would be affected was not explicitly detailed. One study suggests that the breast tissue of this
age group is more sensitive than that of older women. Using this data format, one would then
most likely see a sharp increase at around this birth cohort, but rather one sees a gradual increase.
As a result, this one event cannot entirely be responsible to what is being seen historically
(Wanebo et al., 1968; McGregor et al., 1977; Tokunaga et al., 1979). But later to be seen with
leukemia cases, the population affected would have to be studied to seriously consider this event
as a significant precursor to deaths from breast cancer. And if proven true, this could very well,
be a contention that the younger women exposed during this period would reflect an increasing
number of deaths.

4.1.4 Prostate cancer

Prostate cancer is the second leading cause of deaths in American males. It has been on a
constant rise this century. However, the number of deaths is over three times that of Japan. In
the graphs provided, there is a distinct difference on the prevalence of the disease in each
country. What is amazing about the findings is that where prostate cancer is slightly decreasing
at middle-age groups in the US, there is a sharp increase in later age groups which could be
attributed to better therapy, extending their lives. Additionally, there seems to be a constant
increase in the deaths seen in Japan for all age groups.

As the case is with breast cancer, there has been speculation to the contribution of dietary fat to
this increase in mortality. Migrating data have shown that the Japanese, who have one of the
lowest incidence rates of prostate cancer in the world, and when migrate to places with higher
incidence, increase their risk of developing prostate cancer. Studies have shown that the
incidence rate of Japanese in Hawaii indeed increases to that of native Japanese for first-
generation immigrants (Wynder et al., 1971). Thus, the idea of the environment playing a role in
its etiology is of great interest. Although there have been studies that have investigated such socioeconomic factors such as sexual activity, past history of venereal disease, and the number of children, there has been conflicting data concurring these suppositions (Steele et al. 1971, Krain 1974, Armenian et al. 1975, Greenwald et al. 1974). In addition, there have been numerous reports pursuing the diet angle, and examining foods that may be responsible for an increased risk of prostate cancer. Such examples of these include meat, fish, eggs, and dairy items. But the effect of fat consumption has been the focus of highest speculation.

Even though there has been conflicting reports to the effects of fat consumption, there is the idea of dietary fat and prostate cancer focusing on specific fatty acids, which are of animal origin rather than vegetable origin (Rose and Connolly, 1992). In their review they conveyed that certain fatty acids may be stimulators of cancer cell growth and others acting as inhibitors. Such examples were done in experiments using LA, an n-6 polyunsaturated fatty acid (PUFA) and docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), two n-3 fatty acids. The results showed that LA stimulated growth of the cancer cells and the n-3 fatty acids inhibited its growth. The report added that this may be linked to therapy, where these results could possibly be applied to decreasing the effect of prostate cancer, which have been shown to be in a latent state, and thus no overt signs of the disease is ever noticed until death (Breslow et al., 1977). Unfortunately, as interesting as this research may provide another perspective in explaining the cause of prostate cancer, examination of different fats must be done in both countries to identify if such a theory holds.

One study, however, took a different step in this campaign, and looked at the p53 mutational spectra of prostate cancers in Japan and the United States (Watanabe et al., 1997). Their results showed distinct differences in mutations seen in each country. Where Americans and Europeans had a large percentage of transitions in p53, Japanese had a prevalence of transversions. This result establishes that there could be differing factors, that can play a role in the development of prostate cancer, and such may explain the different rates seen between both countries as identified in the data sets. Nevertheless, the reason for the increase in Japanese deaths has yet to be identified. It is possible that a conglomeration of these ideas may be the answer.
4.1.5 Pancreatic cancer

Pancreatic cancer is the cancer with the lowest 5-year survival rate, which currently is at 3-4%. Because it is normally detected at an advanced stage, effective treatment is naturally futile. What is curious about this disease with the data sets is the most similar trends seen in both the United States and Japan. At earlier age groups, there seems to be an equal number of deaths in both countries of around 0.5-3 and 0.3-1.5 deaths per 100,000 for males and females, respectively. However, there is a switch in the increase of pancreatic cancer deaths in the middle age to older age groups. Whereas both countries show an increase, there is a lag time for this increase in JM and JF compared to that of EAM and EAF. This may help suggest that there is indeed an environmental factor associated with this lag time where Americans seem to indicate an increase before documented data (birth cohort 1858) and the Japanese follow with a steep increase for birth cohort 1879.

To this day, there has been no firm attachment of any etiologic agent to the cause of pancreatic cancer. From diet to working conditions, numerous studies have shown correlations to pancreatic cancer, but only weak associations at that. However, a risk association to smoking has been suggested as a means to the increase in its mortality. But as the case with lung cancer in the United States, the effects of smoking would be naturally seen in the data, yet with pancreatic cancer this effect is not seen. What is seen is sharp increases in both the American and Japanese data, and what is amazing is that the increase is seen from the beginning of recorded data, that of the 1860 birth cohort for 70-74 EAM and EAF and 1889 for 70-74 JM and JF. The only difference is that in the 1980s, both curves converge, and both Japanese genders then surpass EAM and EAF. What may be evident here is that genetic factors may dictate the evolvement of pancreatic cancer. It is possible that the effects of “westernization” may have spurred and compounded the situation in Japan. The data, however, does not agree to what is seen with lung cancer, thus the smoking hypothesis cannot be validated.

It has indeed been investigated that certain environmental factors, most notably, coffee and a high intake of fat, may play roles in the development of pancreatic cancer (MacMachon et. al.
1981, Binstock et. al. 1983, Durbec et. al. 1983, Stensvold and Jacobson 1994). But again, the mentioned factor of smoking should seriously be reviewed, since the data sets do not show lags in the disease by EAF and the same cannot be said of JM and JF. Also, improvement in diagnosis of pancreatic cancer may partially explain the increase in mortality via better documentation of the disease, thus being responsible for the increasing number of deaths.

4.1.6 Stomach cancer

When one is asked about which cancer shows an axiomatic difference in mortality deaths between the United States and Japan, the answer is undoubtedly the cancer of the stomach. Stomach cancer is the most prevalent cancer in Japan, and in the United States, where in the beginning of the 20th century was one of the leaders in mortality, has now become one of the least seen. The peculiar cause of what dictates its intense appearance in Japan has stifled many scientists this century. However, in 1982, the discovery of the bacterium, *Helicobacter pylori*, by Warren and Marshall has actually defined a new perspective to this cancer’s possible origin. Nevertheless, other theories such as the advent of refrigeration, salt consumption, and a vegetable and fruit-based diet are also used to explain the trends seen for stomach cancer in the United States.

As for the trends seen in both the United States and Japan, one only has to look at the graphs to mirror generalizations in numerous studies. In every age group, there has been a decreasing trend in the observed deaths seen for EAM and EAF from the beginning of the century until a constant number is reached at the later birth cohorts. Ironically, with so much emphasis on the high mortality rate seen in Japan, there has actually been a significant drop of observed deaths in all age groups. Not a gradual decline as in the European Americans, this decrease is more steep and begins at exactly 1961 (birth cohort 1889) for all age groups. So the question that arises is the cause to this decreasing trend?

Since European Americans have been experiencing this gradual decrease since around 1930 with birth cohorts dating back to approximately 1880, there has been the idea that the advent of the
refrigerator may have played a major role in this decrease. Before refrigeration, meat products which were and still are a main source of the diet of the average American, were doused with nitrate as a preservative. Nitrate can then be converted to nitrite and eventually be converted to $N$-nitroso compounds which have a detrimental effect on the gastric mucosa. Thus, with the arrival of refrigeration, nitrate use was practically eliminated and provided a healthier product for the consumer. In addition, there has been the idea that a diet including more fruits, vegetables, and fiber may be suspect to the decrease in stomach cancer in the United States. With the push of such a diet in the 1980’s, this may have been true, but data from the Department of Commerce shows that the consumption of fruits and vegetables has actually decreased in the past century (Kurian, 1994). Still, the consumption of fruits high in Vitamin C which provides its reduced form of ascorbic acid does protect the gastric mucosa from $N$-nitroso compounds. Of course, the introduction of Helicobacter pylori also brings a new dimension to this story, but as of right now, it’s effects on birth cohorts from the late 1800’s for Americans has still to be uncovered to make any speculative theories. Thus, there still exists no firm conclusion on the matter.

Japan, on the other hand, does not display the same circumstances seen in the United States. Albeit that refrigeration may have arrived later than in the United States via the Meiji Restoration, such an event does not persuade a decrease in stomach cancer before 1961 as seen in the graphs. Additionally, the use of refrigeration would not alter the preserving of meat, where “fresh” meat was only sold to customers (Longworth, 1983). Ironically, there actually is an upswing in the mortality due to stomach cancer. And what has been mostly used as an explanation is the use of salty products (Tatematsu et. al. 1975). Although this has been a highly researched idea, salt is still just one explanation for the high rate of stomach cancer in Japan. However, the decline in stomach cancer seen in Japan after 1961 seems to be more to do with therapy than with actual environmental causes. With the introduction of mass screening at around this time by the Japanese government, there began a revolution of early diagnosis. Concomitantly, there was also the introduction of the definition of early gastric cancer, defined as cancer limited to the gastric mucosa and submucosa, by the Japanese Society of Gastroenterological Endoscopy. In this respect, physicians now screen patients for this condition and treat it successfully where before it was denoted as an ulcer and treated as such. Since
stomach cancer is the leading cause of cancer deaths in Japan, the government has sponsored yearly examinations for high risk Japanese to uncover any abnormalities before it is too late (Dr. Robert Schapiro, personal communication). Therefore, such a strong push for early diagnosis seems to correspond to what is seen in the mortality graphs. Moreover, this early screening is evident by the 5-year survival rate seen in Japan as compared to the United States, where it is 50% and 15%, respectively (SEER 1992, NCC of Japan 1998). Unfortunately, this does not entirely explain the increase seen before 1961, but with what trends can be seen for different age groups and providing a focus for more extensive studies, a first step can now possibly be further explored to elucidate such answers.

4.1.7 Ovarian and cervical cancers

As the case with prostate cancer in men, ovarian cancer in women has been linked to fat consumption. The issue which arises is the elevated production of estrogens and gonadotropins, which have been theorized to promote the proliferation and malignant transformation of an inclusion cyst of the ovarian surface epithelium (Cramer and Welch, 1983). Therefore, the focus has been placed on fat consumption rather than the common association between most ovarian cancer victims, which is obesity. Nonetheless, its inclusion is one of relative risks where obesity has yet to be entirely accepted and quantified.

Examining the female data for both European Americans and Japanese, one sees unusual trends for Americans, but a unequivocal increase in mortality for Japanese. In the United States, EAF show an increase in deaths up to approximately 1970 (birth cohort 1889), but then drop off for the early age groups. Yet for the older age groups, 60-64 and 70-74, no drop is seen, but a continuous increase in mortality. What studies have suggested about the increase in Japanese mortality is the increase in fat consumption. However, what is being seen in the United States is a curious situation.

What is peculiar about the data set for the EAF is the decrease seen after 1970. An attempt to identify this decrease is taking the idea of increased estrogen being responsible for the increased
risk of ovarian cancer. Studies have indicated that with an increased number of pregnancies or live births, a decrease of ovarian cancer risk is observed (Cramer et al., 1983). Being the case, one can suggest that the period between 1945-1960, the “baby boom” era period, may have had a significant impact on ovarian cancer mortality, but this is only speculation. Additionally, according to Ries, survival for ovarian cancer is higher for women under 45 at 70% than women over 75 at less than 20% (1993). This can then suggest that treatment at younger ages may be more effective than at older ages, and thus explaining the decline in deaths for the early age groups. Nevertheless, an in-depth analysis in identifying the circumstances that lead to these examinations is needed, and possibly question the ideas of fat consumption and obesity as causes to what is found for both American and Japanese data.

The other main reproductive type of cancer is that of the cervix uteri, and thus is included in this discussion with ovarian cancer. In this case, the lower part of the uterus identifies the place of disease. This is one unique cancer where screening of the disease has made a deep impact in the mortality rate of numerous countries. Although such an advancement tool is available, its use is not entirely taken advantage by all women. However, for those who do, the results represent a matter between life or death. To better illustrate this impact, an examination of the data sets is warranted.

As indicated by all age groups, the mortality seen in the United States is a gradual decrease from around 1952 of women born in 1880. This coincides with the period after the “Pap smear” by George N. Papanicolaou was fully recognized and distributed. With the advent of this test, it’s transfer across national boundaries is naturally assumed. And as indicated in Japan, the graphs show that the same trend is seen in all age groups as well. However, what is unique about these graphs is a sharp increase at around 1952 in JF. This could be attributed to a better diagnosis of cancer cases via the “Pap smear” or a underestimation of deaths, but further investigation is warranted to determine this deviation. But like the American data, mortality deaths decrease afterwards. Additionally, another aspect of these graphs is the similar number of deaths being experienced by both countries. These similar trends suggest that after 1952, the environment
being experienced by both countries must be similar which eventuate in similar mortality rates and suggests not to be genetically-based.

Coincidentally, the use of the “Pap smear” combats the unknown presence of an etiologic agent to cervical cancer. What has been of importance to the scientific community is the association of cervical cancer to the human papillomavirus (HPV), namely types 16, 18, and 33. This virus has been identified as an etiologic agent to cervical cancer where this virus was found when examining women with cervical cancer. Conversely, the examination of normal cervices resulted in a low incidence of HPV. The contraction of this virus is usually through sexual intercourse, where the number of sex partners and the age when sexual activity began determines the increased risk of contracting the virus, and in turn increasing the risk of cervical cancer. However, an indication of this virus to prove the decrease in deaths in Japan for cervical cancer would be futile since the prevalence in Japan has been shown to be rather low and the history of cervical cancer cases involving HPV is not documented (Paez et. al. 1996, Nishikawa et. al. 1991). Nevertheless, the latent period to which this virus spends before cervical cancer can be diagnosed may explain an increase in future cases, but that would most likely be seen in incidence and not mortality (Vizcaino et. al. 1998). Although this new etiologic agent may seem to provide an alternative explanation to incidence data, mortality data may rely on the “Pap smear” as the reason to the decreases seen in both data sets. Nevertheless, compiling data of “Pap smear” use is the only effective way to confirm this causal relationship.

4.1.8 Non-Hodgkin’s lymphoma

A disease of the lymphoid tissue, non-Hodgkin’s lymphoma is one cancer that is as apt to arise in children as in adults. As a component of the immune system, lymphoid tissue is susceptible to this type of cancer when an infection arises, most notably through the HIV virus or Epstein-Barr virus, and when the immune system is suppressed. In addition, familial factors, other means of immune suppression, and exposure to industrial solvents have all been targeted as causes to the incidence of non-Hodgkin’s lymphoma. However, as with nearly all cancers, no firm cause has been confirmed to its existence.
It’s effect on mortality is very interesting to say the least. If one takes a look at all age groups to see its historical footprint, there is a very obvious difference in its presence in Japan to that of the United States. Whereas both EAM and EAF show a drastic drop in deaths for birth cohorts 1898 (calendar year 1970) for all age groups, there seems to be an increase in the disease for both JM and JF. But one should take caution to this drop where it may not be wholly attributed to an environmental factor, but rather therapy and/or poor documentation. Moreover, the increase in the Japanese is more pronounced at later age groups (i.e. 60-64 and 70-74). It seems that whatever happened in the United States in 1970 played a major role in the decrease of non-Hodgkin’s lymphoma deaths. Yet, this event isolated its effect from reaching Japan.

As mentioned before, there have been numerous studies in identifying correlations with an increased risk of contracting non-Hodgkin’s lymphoma. In these attempts, relative risks establish these links. Nevertheless, it is second nature to believe that a suppressed immune system would indeed increase the risk. One study discusses this idea with emphasis on the elderly, where suppression may be enhanced and thus provides reason to believe that the disease, most notably the B-cell type, can be age-dictated (Potter, 1992). Alternatively, there is another focus targeting the HIV virus and it’s new role as a possible cause. Unfortunately, this same focus on viruses has been spotlighted on the Epstein-Barr virus with negative results. With this virus’ high prevalence in society, it’s role as a primary cause to the increase in non-Hodgkin’s lymphoma has been ruled out (Hartge and Devesa, 1992). But the increase seen in both JM and JF may be explained by an entirely different virus named HTLV-1, which is prominent in certain areas of Japan which have a higher incidence of non-Hodgkin’s lymphoma (Takatsuki, 1995). In contrast, the sharp drop seen in the United States may actually be due to the advent of chemotherapy at exactly the time the drop in mortality is seen. With five-year survival rates of over 50% in adults and approaching 75% in children in the 1980’s, this medical breakthrough may explain such a drop. What these graphs indeed indicate is that Americans born after 1898 show a decrease susceptibility to death from this disease. Additionally, the Japanese are experiencing a different environment which is resulting in a higher mortality rate.
4.1.9 Leukemia

The disease of bone marrow and blood, leukemia entails low counts of red blood cells, white blood cells, and platelets. As a result, there are signs of anemia, an inability to ward off infections, and easy bleeding and bruising. The focus on leukemia have mostly been placed on children; however, most cases actually occur in elder adults aged 60 and older. It is expected that the disease will strike 10 times the number of adults than children in 1998 (Leukemia Society of America, 1998). But curiously, there is no clear indication to what causes the disease to develop. Such ideas are exposure to benzene in the workplace, and more notably, repercussions from irradiation.

When examining the graphs comparing mortality data between Japan and the United States, increasing trends are seen for both countries. In addition, the number of deaths are indeed higher in the United States than in Japan. Yet, a very unique consistency in these graphs show a leveling off of deaths in the United States after the mid 1960’s (birth cohort mid-1890’s) and leveling off, whereas in Japan, this is evident at birth cohort 1910. One can then ask what may be responsible for the change in slope for the American data, and the lagging treatment seen in Japan? As the case with non-Hodgkin’s lymphoma, the advances in science is one avenue to explore.

In the United States, the advent of chemotherapy began a new dimension in treating all types of cancer. Remarkably, the Leukemia Society of America indicates that the survival rate for acute lymphocytic leukemia has actually increased from 4% in 1960 to 80% in 1993 (1998). Of course, claiming this as a significant percentage of leukemia cases need to be validated. Such a leap in science has proven how lives can be saved with the miracles discovered everyday. Unfortunately, this does not coincide with the somewhat consistent number of deaths seen in EAM and EAF. If therapy was the sole reason, then there would actually be a decrease in leukemia deaths, but as the graphs indicate, that is not the case. What could help explain this situation is the increased incidence of leukemia cases in the past quarter century. With a consistent number of deaths, a higher incidence of cases provide a higher probability of deaths occurring. Thus, the number of deaths rely on a greater number of victims compared to previous
years. Consequently, a complementation of the two (therapy and increased incidence) result in no change of deaths. Determining incidence cases and comparing to mortality deaths in birth cohorts after 1895 is what further studies can explore. As the LSA reports, the increase in incidence is indeed the case (Leukemia Society of America, 1998).

But why the lagging steady number of cases in the Japanese? One important event which warrants mentioning is the dropping of atomic bombs on Nagasaki and Hiroshima. Reports that have investigated this event have followed individuals affected from the bombings. However, they are unable to determine whether the numbers are accurate, where an increase in leukemia-causing deaths cannot be correlated to a specified amount of radiation exposed to these citizens (Jablon et al., 1971; Schull, 1996). To compound its unlikeness to contributing to any increase in leukemia is the fact that these two cities do not constitute a significant part of the population. This naturally could be argued however that a high percentage of deaths from this group can alter the country’s death rate, but from the studies that have investigated these cases, nothing can be confirmed to the bombing’s effects on the whole affected population.

Although technology transfer and advances in Japan could be seen as consistent with the United States, there was a recent discovery which may help explain the trend seen in JM and JF. In 1977, adult T-cell leukemia was first identified in Japan. This type of leukemia is the result of the etiologic agent, human T-lymphotropic virus, better known as the HTLV-1 virus (Takatsuki, 1995). This virus is the first retrovirus to be associated directly with human malignancy. Therefore, its prevalence in certain parts of Japan has warranted HTLV-1 antibody testing for donated blood since November 1986. Additionally, it can be transmitted through sexual intercourse from male to female. This retrovirus, which has been also documented in the Caribbean islands and parts of Central Africa, may be the key component to the increasing trend seen in Japan, since chemotherapy is rendered not effective. Like the HIV virus, with it’s recent discovery, determining whether this virus could have played a role with birth cohorts before 1900 will be difficult to ascertain, but would be beneficial nevertheless. For birth cohorts after 1910, it is possible that medical care could have improved or another environmental factor can be responsible for the halt to this increasing trend.
4.1.10 Brain cancer

Determining one etiologic agent to the cause of brain cancer, which comes in various forms, has been unsuccessful. Various studies have shown therapeutic ionizing radiation to the head and trauma to the head as two causes which can initiate the development of brain cancer. However, there are other suppositions by other studies which suggest reason to look further outside of the previous scope. Most notably is the suggestion that electromagnetic waves may be responsible in causing brain cancer. In the past decade, research has also made breakthroughs in the area of genetics by identifying genetic changes in brain tumors. Such examples are the losses of genetic material on chromosomes 10 and 17 in astrocytomas and the partial or total loss of chromosome 22 in meningiomas.

When analyzing the data to these suggestions for etiology, there seems to be no serious changes in mortality for Japanese. For EAM and EAF, there is a definite increase in mortality for older age groups (60-64 and 70-74), but a steady number of deaths for younger and middle-age groups. The difference in mortality between both countries is great, although the number of deaths is small compared to other cancers. For the 70-74 age group, there is an increase in EAM and EAF from around 5 in the 1880 birth cohort to above 20 in EAM and a little over 15 for EAF for the 1920 birth cohort. In terms of electromagnetic waves, attributing this increase to the installation of electricity in the average home would seem to show similar effects in Japan. Where nearly 100% of American homes had electricity around 1950 and Japan following suit, one would suspect the same in the Japanese data, but that is not the case.

Although industrially, Japan did gain it's advanced equipment much later than the United States, in terms of electricity, it's incorporation in Japanese society was similar where documents indicate its use dating back to 1903 and increasing thereafter (JSA, 1987). Thus, if the argument is made that these increases in mortality for older Americans is due to electromagnetic waves, then this would also be the case with older Japanese, yet the mortality rate does not surpass 2 deaths per 100,000 for all birth cohorts, both male and female. To compound these data results, there have been several studies that disagree with the hypothesis of electromagnetic waves. In
several studies, evidence showing a causal link between electromagnetic waves and brain cancer is weak at best (Harrington et. al., 1997; Johansen and Jorgen, 1998; Sahl et. al., 1993, Tynes et. al., 1994). In Japan, the dropping of the atomic bombs on Hiroshima and Nagasaki have also sparked interest in possibly causing an increase in brain cancer; however, no such link has been made. (Schull, 1996) The data does seem to dismiss that electromagnetic waves may be the cause to this increase in EAM and EAF, but does suggest that the new findings on the genetic makeup of tumors brings up the issue of possible genetic differences between both nations. However, studies to pursue this is warranted to explore this path in explaining the data.

4.2 Further analysis of lung cancer via smoking

To better illustrate the advantages of the format in which Japanese mortality data has been assigned, an example of what can be done with lung cancer data will be explored. As the case with any possible environmental factor, it is one thing to say it is responsible for one form of cancer and it is another to prove it. With the case of lung cancer, however, it seems that the connection with cigarette consumption is very much accepted in the scientific community. Nevertheless, it is of much interest to this same community to establish a linear relationship between the two. As an example to what can be done with the Japanese data to achieve this, results from investigating cigarette consumption in the United States, and lung mortality will be discussed.

As the case with each environmental factor, the historical picture of it’s presence in society is important in correlating with the age-dependent birth year cohort-specific mortality. This is the approach to take in terms of cigarette smoking, and involves the percentage of smokers of different birth cohorts and relating such information to the mortality data for lung cancer. Using the Extended Knudson-Moolgavkar model developed by Herrero-Jimenez, it is now possible to determine the subpopulation at risk for a site-specific cancer deemed by the variable, F. His
Figure 9: Percentage of Smokers vs. Subpopulation at Risk for Lung Cancer for EAM and EAF, Birth cohorts 1820-1920.

\[ F_{\text{lung}} \text{ vs. } F_{\text{cigarette}} \]

\[ F_{\text{lung}} = C F_{\text{cig}} - 0.16 C F_{\text{cig}} + 0.16 \]

\[ C = 0.95 \]

(Herrero-Jimenez, personal communication)
mathematical model, which involves two mutations for initiation of an adenoma and a third to progress to cancer, is based on the American mortality curves through age-dependent birth year cohort-specific mortality with an appreciation for the biology involved in developing cancer (Herrero-Jimenez et al., 1998). This attempt to model cancer is a method to establish links between historical environmental changes and the mortality trends one identifies. With similar mortality curves seen in Japan, this model is essential in providing similar information. As a result, the following graph gives strong evidence to the cause and effect situation between cigarette smoking and lung cancer: As the graph indicates, there is a linear relationship between the fraction of the population that smoked for birth cohorts 1820-1920 and the calculated subpopulation at risk for lung cancer. This evidence indeed illustrates that this data format provides a strong connection between the historical findings for environmental factors and it’s effects on cancer mortality.

It is this approach which can eventually be done with the Japanese data alongside detailed smoking percentages of the population for different birth cohorts. As early indications show, there is a peak percentage for male smokers to be slightly above 80 and females wavering at around 15%. It will be interesting to see whether the same linear relationship will be seen with what has been conveyed by the mortality curves. As figure 10 retells what was seen before, the sharp increases seen in Japanese males mirrors that of European American males. However, the same cannot be said between Japanese females and European American females. Such differences will be fully understood when the percentage of smokers in Japan is compared to the calculated subpopulation at risk for lung cancer from the Extended Knudson-Moolgavkar Model.
Figure 10: Birth Cohorts vs. OBS(t) per 100,000 for Lung Cancer (Age group 70-74) for EAM, JM, EAF, and JF
5. CONCLUSION

The method used to convey the raw mortality data provides a better means of determining the environment's effects via birth cohorts and the industrial changes that took place in Japan after the United States. The Meiji Restoration, as stated earlier, did bring Western culture to Japan, and it's effects may be responsible to what is seen from the data sets. The consistent mentioning of increased fat consumption to explain several cancers is indeed something to investigate, but with the increasing trends indicated, it is now possible to pinpoint when such fat intake must have increased to cause said increases. What is curious, however, is the relationship that smoking has had on lung cancer for both nations. It is well known that smoking is responsible for lung cancer deaths in the United States, but confirming this in other countries have not been scrutinized via birth cohorts. Since manufactured cigarettes were mass produced from 1904, signs from the effects of tobacco in Japan is well displayed with respect to American males. However, more exact consumption data for birth cohorts need to be uncovered to determine a linear relationship as seen with the American data. Further, what is currently known from available smoking data, the low percentage of Japanese female smokers may reflect the insignificant increase in lung cancer mortality since birth year 1880. Nevertheless, the first step has been achieved where the birth cohorts of 1880 and beyond seem to have been affected for both genders. Continuing these efforts, the highest prevalence of smokers seen in the late 1960's should expect a peak number of deaths from lung cancer in the future. Thus, the data set analyzed via birth cohorts and the comparative analyses of certain selected cancers do indicate that cultural differences validate a role in the differences in mortality curves for both nations. Additionally, deaths from lung cancer in Japan can be attributed to cigarette use which mimics the lung cancer trends seen in the United States albeit a lag due to the initial presence of widespread cigarette consumption. Moreover, with this more effective look at lung cancer mortality, the groundwork has been set up to determine a linear relationship with smoking as seen with the American data.
6. FURTHER SUGGESTIONS FOR RESEARCH

As detailed in this paper, the most effective means in establishing links between environmental factors and the changes seen in mortality curves is to provide age-dependent birth year cohort-specific data. A new understanding can better be achieved where trends once seen with age-adjusted death rates are simply a means of noticing a trend by calendar year with no account of birth year. Consequently, this new setup for the Japanese mortality data shows a clearer picture to what years are involved that may indicate effects from an environmental change. As well, perusing any age group and their birth cohorts can then identify precisely which birth cohorts seem to be affected the most.

Coincidentally, this new format, as shown for lung cancer and cigarette smoking can also be applied to other cancers in the database. Such examples are colon cancer, breast cancer, and prostate cancer, where diet has been identified as a possible cause to changes in mortality. With identification of what years such changes occur, and using data of changing diet from these birth cohorts, one can explore the possibility of linear relationships from the modeling techniques described before. It is the involvement of this format, mathematical modeling, and detailed environmental data by birth cohort that will begin the necessary determination of the cause and effect of environmental factors. As a result, a new understanding for the curtailing and eventually, prevention of site-specific cancers can be possible.
7. REFERENCES


Herrero-Jimenez, Pablo. personal communication.


Schapiro, Dr. Robert. personal communication.


Appendix A

Age vs. OBS(t) Graphs
Appendix B

Birth Cohort vs. OBS(t) Graphs
Birth Cohort vs. OBS(t) for Lung Cancer in EAM and JM

Birth Cohort vs. OBS(t) for Lung Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Lung Cancer in EAM and JM

Birth Cohort vs. OBS(t) for Lung Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Lung Cancer in EAM and JM

Birth Cohort vs. OBS(t) for Lung Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Lung Cancer in EAM and JM

Birth Cohort vs. OBS(t) for Lung Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Colon Cancer in EAM and JM

Birth Cohort vs. OBS(t) for Colon Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Colon Cancer in EAM and JM

Birth Years vs. Obs(t) for Colon Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Colon Cancer in
EAM and JM

Birth Cohort vs. OBS(t) for Colon Cancer in
EAF and JF

Birth Cohort

OBS(t) per 100,000

0 10 20 30 40 50 60
1860 1870 1880 1890 1900 1910 1920 1930 1940 1950 1960

Birth Cohort

OBS(t) per 100,000

0 10 20 30 40 50 60
1860 1870 1880 1890 1900 1910 1920 1930 1940 1950 1960

Birth Cohort

62.5-Japan
62.5-USA

62.5-Japan
62.5-USA
Birth Cohort vs. OBS(t) for Colon Cancer in EAM and JM

Birth Cohort vs. OBS(t) for Colon Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Rectal Cancer in EAM and JM

Birth Cohort vs. OBS(t) for Rectal Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Rectal Cancer in EAM and JM

Birth Cohort vs. OBS(t) for Rectal Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Rectal Cancer in EAM and JM

Birth Cohort vs. OBS(t) for Rectal Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Breast Cancer in EAF and JF

Birth Cohort

32.5-Japan
32.5-USA

Birth Cohort

42.5-Japan
42.5-USA

Birth Cohort
Birth Cohort vs. OBS(t) for Breast Cancer in EAF and JF

Birth Cohort vs. OBS(t) for Breast Cancer in EAF and JF

Birth Cohort vs. OBS(t) for Breast Cancer in EAF and JF

Birth Cohort vs. OBS(t) for Breast Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Breast Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Prostate Cancer in EAM and JM

Birth Cohort vs. OBS(t) for Prostate Cancer in EAM and JM

Birth Cohort vs. OBS(t) for Prostate Cancer in EAM and JM

Birth Cohort vs. OBS(t) for Prostate Cancer in EAM and JM
Birth Cohort vs. OBS(t) for Prostate Cancer in EAM and JM

Birth Cohort

OBS(t) per 100,000

1850 1870 1890 1910 1930

- 72.5-Japan
- 72.5-USA
Birth Cohort vs. OBS(t) for Pancreatic Cancer in EAM and JM

Birth Cohort vs. OBS(t) for Pancreatic Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Pancreatic Cancer in EAM and JM

Birth Cohort vs. OBS(t) for Pancreatic Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Pancreatic Cancer
in EAM and JM

Birth Cohort vs. OBS(t) for Pancreatic Cancer
in EAF and JF
Birth Cohort vs. OBS(t) for Stomach Cancer in EAM and JM

Birth Cohort vs. OBS(t) for Stomach Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Stomach Cancer in EAM and JM

Birth Cohort vs. OBS(t) for Stomach Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Stomach Cancer in EAM and JM

Birth Cohort vs. OBS(t) for Stomach Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Stomach Cancer in EAM and JM

Birth Cohort vs. OBS(t) for Stomach Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Stomach Cancer in EAM and JM

Birth Cohort vs. OBS(t) for Stomach Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Ovarian Cancer in EAF and JF

Birth Cohort vs. OBS(t) for Ovarian Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Ovarian Cancer in EAF and JF

Birth Cohort vs. OBS(t) for Ovarian Cancer in EAF and JF

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Birth Cohort vs. OBS(t) for Ovarian Cancer in EAF and JF

Birth Cohort vs. OBS(t) for Ovarian Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Ovarian Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Cervical Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Cervical Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Non-Hodgkin's Lymphoma in EAM and JM

Birth Cohort vs. OBS(t) for Non-Hodgkin's Lymphoma in EAF and JF
Birth Cohort vs. OBS(t) for Non-Hodgkin's Lymphoma in EAM and JM

Birth Cohort vs. OBS(t) for Non-Hodgkin's Lymphoma in EAF and JF
Birth Cohort vs. OBS(t) for Non-Hodgkin's Lymphoma in EAM and JM

Birth Cohort vs. OBS(t) for Lymphoma in EAM and JM
Birth Cohort vs. OBS(t) for Non-Hodgkin's Lymphoma in EAM and JM

Birth Cohort vs. OBS(t) for Non-Hodgkin's Lymphoma in EAF and JF
Birth Cohort vs. OBS(t) for Leukemia in EAM and JM

Birth Cohort vs. OBS(t) for Leukemia in EAF and JF
Birth Cohort vs. OBS(t) for Leukemia in EAM and JM

Birth Cohort vs. OBS(t) for Leukemia in EAF and JF
Birth Cohort vs. OBS(t) for Leukemia in EAM and JM

Birth Cohort vs. OBS(t) for Leukemia in EAF and JF
Birth Cohort vs. OBS(t) for Leukemia in EAM and JM

Birth Cohort vs. OBS(t) for Leukemia in EAF and JF
Birth Cohort vs. OBS(t) for Brain Cancer in EAM and JM

Birth Cohort vs. OBS(t) for Brain Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Brain Cancer in EAM and JM

Birth Cohort vs. OBS(t) for Brain Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Brain Cancer in EAM and JM

Birth Cohort vs. OBS(t) for Brain Cancer in EAF and JF
Birth Cohort vs. OBS(t) for Brain Cancer in EAM and JM

Birth Cohort vs. OBS(t) for Brain Cancer in EAF and JF