DETAILED DESCRIPTION OF WISCONSIN CANCER MORTALITY DATA

(By Site and Sex: 1970 - 1975)

Steve Dahlberg

UNIVERSITY OF WISCONSIN—MADISON
DETAILED DESCRIPTION OF WISCONSIN CANCER MORTALITY DATA
(By Site and Sex: 1970-1975)

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February 1980

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Research supported in part by the Wisconsin Clinical Cancer Center under NIH grant NIH-R01-CA-16405
ACKNOWLEDGEMENTS

I would like to express my deepest appreciation to Dr John Crowley, Director of the Biostatistics Unit, for providing guidance and encouragement.

The Wisconsin Mortality data was gratefully provided by the Bureau of Health Statistics, Division of Health, Wisconsin Department of Health and Social Services. Mr Scot Moss, of the Bureau, was instrumental in providing advice concerning this data.

Thanks are also extended to Phyllis Multhauf, Lou Ann Stittleburg and Debbie Powers, who contributed to the preparation of this manuscript; and also to Robin Fox, Bill Cooper and Dr Tony Camilli, who provided useful summaries of current epidemiological reviews of specific cancer sites.

Finally, I would like to express my appreciation to Diane Stegner-Lowell for the organization, editing and typing of the text.
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HIGHLIGHTS

For both males and females highly significant differences have been found between Wisconsin counties regarding mortality from all malignant neoplasms combined.

- Counties in western Wisconsin tend to have lower cancer mortality, while those in the southeastern corner of the state, as well as those in the north and north central regions, tend to have higher rates.
- Areas of high and low mortality are more clearly differentiated for female cancer than for male cancer.

Highly significant differences in site specific cancer mortality risks between Wisconsin counties were found for the following:

- Male stomach cancer
- Male colon cancer
- Male lung cancer
- Female rectal cancer
- Cervical cancer

Geographical clustering of counties with high or low cancer mortality risks were found for the following sites:

- Male stomach cancer: areas of higher mortality in the southwestern and southeastern corners of the state
- Male lung cancer: areas with lower mortality in the west central part of the state
- Female rectal cancer: higher mortality seen in the north central part of the state
- Cervical cancer: areas of lower mortality in the south central and northwestern parts of the state
- Female bladder cancer: areas of lower mortality in the north and north central part of the state.

Age and site specific cancer rates for Wisconsin are generally quite similar to the corresponding national rates with the exception of cervical cancer. Wisconsin's cervical cancer mortality rates are lower than those for the entire United States.
Secular trends from 1970 to 1975 in Wisconsin's site and sex specific, age adjusted cancer mortality rates are consistent with national trends. The following trends have been observed in Wisconsin's rates:

- Significant increases in male lung cancer mortality
- A general rise in female lung cancer and male colon cancer mortality
- Significant decreases in male stomach cancer mortality
DETAILED DESCRIPTION OF WISCONSIN CANCER MORTALITY DATA
(By Site and Sex: 1970-1975)

The primary purpose of this study is to describe geographical and secular trends of Wisconsin cancer mortality in an effort to generate and verify etiological hypotheses concerning cancer.

a. Statistical modeling techniques have been used to identify geographical areas within Wisconsin with high and low cancer mortality risks. Computer generated maps were produced to aid in the interpretation of the resulting patterns. Nonparametric statistical tests were developed to help in the verification of geographical clusters. Comparisons were made between this data and the 1950-1969 mortality data analyzed by Mason-McKay.¹

b. The US and Wisconsin's cancer mortality experience were compared with regard to age specific rates as well as secular time trends of age adjusted rates. Differences between male and female rates for Wisconsin as well as the entire US have also been examined.

Sources of Data

The principle source of data for this study was the centralized record of death certificates maintained by the Wisconsin Bureau of Health Statistics, Division of Health.² Wisconsin 1970 population figures were obtained from 1970 US census data through the Applied Population Laboratory, University of Wisconsin.³ Wisconsin 1975 population estimates were obtained from the Demographic Services Center, Wisconsin Department of Administration.⁴ National cause specific mortality rates for 1970 were determined using published data from the US Vital Statistics Division,⁵ and the US Bureau of the Census.⁶ Cause specific US cancer mortality rates from 1935 to 1974 were obtained from a paper by Devesa and Silverman.⁷

For a description of the number of cancer deaths by site and sex, the reader is referred to the annual reports Cancer in Wisconsin (year) and Public Health Statistics, Wisconsin (year), published by the Wisconsin Bureau of Health Statistics.

Methods

Age adjusted sex and site specific mortality rates were calculated using the direct method of adjustment. These rates were standardized to the US 1970 or US 1950 census figures as indicated on each graph. Confidence intervals for age adjusted rates as well as for age specific rates were calculated using a standard error estimate described by Chiang.⁸ Age and site specific mortality ratios were calculated in a straightforward manner. The method used to calculate confidence intervals for these ratios is described in Appendix I.
Differences in county cancer mortality was examined using the multiplicative model proposed by Breslow and Day. This model provides an estimate of a revised standardized mortality ratio (SMR) for each county. The standard used to derive revised SMR's is that of the entire state. For each site and sex, this model was fit to the data and a goodness-of-fit test described by Breslow and Day for the model was performed. In all cases the results of this test revealed no reason to believe the models did not fit the data. Variations in county, cause and sex specific cancer mortality risk were evaluated by testing the hypothesis that all of the county SMR values are equal versus the alternative that the county SMR values are not all equal.

Regardless of the results of the tests for overall differences in county mortality, geographical patterns of high or low risk may or may not be discernable. Because of large variations in the size of each county's population, using county SMR estimates alone is not the best way to identify those counties with particularly high or low cancer mortality risks. A county with a small population may have a very high, or low, SMR estimate and still not be significantly different from the other counties, while a county with a large population may have an SMR estimate relatively close to the other counties and still be significantly different from them.

To identify those counties with significantly different cancer risks from the rest of the state, the following statistical test was used for each site and sex. For each of the 72 counties the hypothesis that its SMR value is different from the remaining 71 counties was tested. If this hypothesis is rejected at significance level $\alpha = .05$, the individual county is identified as having a significantly higher, or lower, risk compared to the rest of the state. Because of the large number of hypotheses being tested and the $\alpha$-level, one would expect three or four counties on each map to be identified as significantly different from the rest of the state due to chance alone. For each cancer site and sex a map of Wisconsin was generated indicating each county's SMR estimate. Those counties identified as having an SMR significantly different from the remaining counties as well as those counties with SMR estimates in the top and bottom ten percent of all counties were also identified on each map.

Two nonparametric statistical tests were developed to help verify geographical clustering of counties. These tests determine whether or not the number of pairs of contiguous counties with high, or low, SMR estimates is greater than what might be expected from chance. If for a given cancer site there is a large area of the state with a high cancer mortality risk, then one might expect the number of pairs of contiguous counties both with high SMR estimates to be large. Similarly if there is a large area of the state with low cancer mortality risk, then one might expect the number of contiguous counties both with low SMR estimates to be large.

A description of these tests is given in Appendix II.

Considerations Regarding Mortality Data

A major advantage concerning the use of mortality statistics is that deaths are registered and collected for the entire population. Also mortality statistics have been routinely collected for a considerable length of time -- much longer than most incidence statistics. This enables comparisons to be made between
geographic areas as well as over time. This study is concerned with identifying geographical and secular trends in cancer mortality within Wisconsin.

A major problem with mortality data is that it underestimates the occurrence of disease. Cause specific mortality rates are a function of survival as well as incidence rates. Obviously if a person develops a disease but is cured, the mortality statistics for that disease will remain unchanged. However, even changes in survival rates may influence cause of death statistics as a result of changing the risks for competing causes of death. The amount that cause specific mortality statistics underestimates incidence depends on the particular disease. For those diseases with a rapid clinical course and low survival such as pancreatic cancer, stomach cancer or lung cancer, mortality and incidence statistics might be expected to be similar. For diseases with higher survival rates such as breast cancer or colorectal cancer, mortality statistics may not reflect incidence statistics as clearly.

As more sophisticated diagnostic techniques are developed and used, the distribution of cause of death statistics may change. This can be a result of an improved diagnosis leading to better or earlier treatment and consequently improved survival. Another reason for this may be that a new technique allows a particular disease to be more readily diagnosed hence increasing its reported frequency. Variations in the available medical care may also result in variations in the cause specific mortality risks.

Death certificate information may have spatial or temporal fluctuations as a result of differences in methods of completion. Changes in the cause of death classification schemes as well as the methods used to determine the underlying cause of death may influence cause specific mortality rates.

Mortality statistics may also be influenced by population migration patterns. If, for example, people with a given disease have a tendency to change their residence in order to facilitate treatment, the corresponding incidence as well as mortality statistics will be affected.
ALL SITES CANCER MORTALITY IN WISCONSIN
1970-1975
ICDA 140-209*

I. RESULTS

A. Sex and age specific mortality rates for all malignant neoplasms in Wisconsin are generally similar to those for the US. However, for both sexes Wisconsin rates tend to be slightly lower than the corresponding US rates between the ages of 35 to 60. Also, for the final age category, 80+ years of age, the Wisconsin rates appear to be higher than the US rates. (Graphs 1 and 2)

B. Age adjusted white US cancer mortality rates between 1935 and 1975 show a consistent increase in male cancer rates and a downward trend with perhaps a leveling off in female rates. Wisconsin sex and year specific, age adjusted all cancer mortality rates are lower than the corresponding US white rates with the exception of the female 1970 rate. (Graphs 3 and 4) The lower male cancer rates in Wisconsin are consistent with the 1950 to 1969 data. The secular trends from 1970 to 1975 within Wisconsin show a continuing increase in male cancer mortality and a decrease in female cancer mortality. (Graph 5)

C. Comparisons between the US and Wisconsin age specific sex ratios show that for age groups over 60 years old the difference between the male and female mortality rates is not as large as it is for the US as a whole. (Graph 6) This is primarily a result of the Wisconsin male mortality rates for these age groups being lower than the corresponding US male rates.

D. Comparison of sex specific, age adjusted mortality rates for the seven Wisconsin Health System Agency areas (HSA's) indicate a significantly higher male rate in HSA-2, the Milwaukee area. The remainder of the male cancer rates seem to be about the same. The female rates also seem to be about equal.

* Underlying cause of death statistics in this report are based on the Eighth revision of the International Classification of Disease, adapted for use in the United States - ICDA 8.
E. For each sex, a multiplicative model proposed by Breslow and Day was fit to the data. This model provides revised estimates of the standardized mortality ratios for each Wisconsin county.

1. A goodness-of-fit test for the multiplicative model indicates that for males there is no reason to believe the model does not fit the data, \( p = .42 \). For females the significance value was small, \( p = .065 \), however not significant at the \( \alpha = .05 \) level.

2. An overall test for differences between the 72 county SMR values indicates for both males and females there are very significant differences between counties, \( p < 10^{-5} \) in both sexes.

3. For each sex, a Wisconsin map was generated indicating the county SMR estimates as well as which counties are significantly different from the rest of the state.

   For females, low SMR estimates are generally found along the western and southwestern parts of the state. Some high SMR estimates are in the northwestern corner of the state. Douglas county was shown to have a high all cancer mortality rate for females using 1950 to 1969 data by Mason et al.¹ This is in agreement with what is seen in the 1970 to 1975 mortality data.

   For males, low SMR's are generally found in the western and southwestern part of the state. The southeastern corner of the state has high SMR estimates. Also there is a group of counties with high estimates in northcentral Wisconsin. The 1950 to 1969 male cancer mortality data shows Milwaukee and Oneida counties with high rates. This is also the case for the 1970 to 1975 data.

4. For each sex, two tests for possible geographical clustering of counties based on the SMR estimate were performed. The first test considers the number of pairs of contiguous counties both with high SMR estimates. For both sexes the number of such pairs was not found to be significantly different than what might be expected from chance. The second test considers the number of pairs of contiguous counties both with low SMR estimates. For males, this number was again found not to be significant. However, for females, the number of pairs of contiguous counties with low SMR estimates seems to be too large, \( p = .003 \). This is a reflection of the group of counties in western Wisconsin with low estimates.
II. DISCUSSION

In the US, male cancer incidence rates have been rising whereas female cancer incidence rates have been declining. Recently the male cancer incidence rate has surpassed the female rate. Examination of the "all cancer sites combined" category alone may be misleading, since it is clear that incident rates for some sites have been rapidly increasing while at the same time others have been decreasing. Also, geographic patterns can be seen for some site specific cancers. In general, when searching for etiologic hypotheses, site specific statistics are more useful than the all site category.

The magnitude of the cancer problem in the US can be examined by various methods. In 1973, there were about 350,000 cancer deaths in the US. In the same year, about 665,000 persons were first diagnosed with cancer. If the mortality and incident rates remain at these levels, about one person in four will develop cancer in their lifetime.

Another method used to assess the magnitude of the cancer problem is the calculation of a measure called Potential Years of Life Lost (PYLL) between the ages of 1 and 70. This measure is a count of the number of years remaining from age at death to age 70 for persons dying of a specific cause. For example, if a person dies of lung cancer at age 55, the person contributes 15 potential years of life lost to age 70. This measure has the effect of placing more emphasis on younger deaths.

For Wisconsin resident deaths in 1970, this measure was calculated for major causes of death. The results are given in Chart 1. For women, cancer is the leading contributor to the PYLL index. For men, accidents and heart disease rank ahead of cancer. Specific sites of cancer were examined from the Wisconsin resident cancer deaths 1970-1975. These results are given in Chart 2. For women, breast cancer followed by ovarian cancer rank highest. For men, lung cancer followed by cancer of the brain and central nervous system rank highest. If the colon and rectum sites are combined, this category would rank second among men.
WISCONSIN RESIDENT DEATHS 1970

Distribution of Potential Years of Life Lost Between Ages 1 and 70 by Cause of Death

Accidents (800-949)

Diseases of the Heart (393-398, 402, 404, 410-429)

Malignant Neoplasms (140-209)

Other Causes

Cerebrovascular Disease (430-438)

Suicide (950-959)

Congenital Abnormalities (740-759)

Influenza and Pneumonia (960-969)

Homicide (960-969)

Cirrhosis of the Liver (571)

Other Diseases of the Circulatory System (440-458)
WISCONSIN RESIDENT SITE SPECIFIC CANCER DEATHS 1970-1975
Distribution of Potential Years of Life Lost Between Ages 1 and 70 by Cause of Death

Lung (162)
Breast (174)
Brain and CNS (191-192)
Colon (153)
Ovary (183)
Lymphatic Leukemia (204)
Pancreas (157)
Myeloid Leukemia (205)
Stomach (151)
Hodgkin's Disease (201)
Kidney (189)
Rectum (154)
Cervix Uteri (180)
Esophagus (150)
Prostate (185)
Corpus Uteri (182)
Bladder (188)
Liver (155)
MAP 2

ALL CANCER SITES
FEMALE WISCONSIN RESIDENTS
1970-1975

SMR Estimate

SIGNIF. TOP DECILE
SIGNIF. TOP HALF
TOP DECILE
NOT SIGNIF.
LOW DECILE
SIGNIF. LOW HALF
SIGNIF. LOW DECILE
ALL MALIGNANT NEOPLASMS

\[ * = \text{WISC. MALE RATE (1970-1975)} \]
\[ \triangle = \text{U.S. MALE RATE (1970)} \]
DOTTED LINES INDICATE 95% C.I. FOR WISC. RATES

GRAPH 1

ANNUAL SPECIFIC MORTALITY RATE PER 100,000

\[ y = 10^x \]

\[ 10^{-2}, 10^{-1}, 10, 10^2, 10^3, 10^4, 10^5 \]

AGE

\[ 0, 10, 20, 30, 40, 50, 60, 70, 80, 90 \]
ALL MALIGNANT NEOPLASMS

\[ * = \text{WISC. FEMALE RATE (1970-1975)} \]
\[ \triangle = \text{U.S. FEMALE RATE (1970)} \]

DOTTED LINES INDICATE 95\% C.I. FOR WISC. RATES

ANNUAL AGE SPECIFIC MORTALITY RATE PER 100,000

\[ 10^5 \]
\[ 10^4 \]
\[ 10^3 \]
\[ 10^2 \]
\[ 10 \]
\[ 10^{-1} \]
\[ 10^{-2} \]

AGE

0. 10. 20. 30. 40. 50. 60. 70. 80. 90
ALL CANCER SITES
FEMALES

* INDICATE WISCONSIN RATE
Δ INDICATE U.S. WHITE RATE

ANNUAL AGE ADJUSTED MORTALITY RATES PER 100,000


U.S. 1950 STANDARD
ALL MALIGNANT NEOPLASMS

* = WISC. MALE RATE
△ = WISC. FEMALE RATE
DOTTED LINES INDICATE 95% C.I. FOR WISC. RATES

ANNUAL AGE ADJUSTED MORTALITY RATE PER 100,000

DIRECTLY STANDARDIZED TO US 1970 POPULATION
ALL MALIGNANT NEOPLASMS

* = WISC. RATIO (1970-1975)
△ = U.S. RATIO (1970)
DOTTED LINES INDICATE 95% C.I. FOR WISC. RATIO

GRAPH 6

MALE RATE / FEMALE RATE

0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00 2.25 2.50 2.75 3.00

0 10 20 30 40 50 60 70 80 90

AGE
ALL MALIGNANT NEOPLASMS

* = WISC. MALE RATE (1970-1975)
▲ = WISC. FEMALE RATE (1970-1975)
BARS INDICATE 95% C.I. FOR WISC. RATES

ANNUAL AGE ADJUSTED MORTALITY RATE PER 100,000

HSA-1 HSA-2 HSA-3 HSA-4 HSA-5 HSA-6 HSA-7

Directly Standardized to US 1970 Population
STOMACH CANCER MORTALITY IN WISCONSIN
1970-1975

ICDA 151.0-151.9

I. RESULTS

A. Sex and age specific stomach cancer mortality rates for Wisconsin are very similar to those for the entire US population. (Graphs 1 and 2)

B. Secular trends from 1935 of age adjusted stomach cancer mortality rates for the white US population indicate a dramatic and continuous decrease for both male and female stomach cancer mortality. The Wisconsin sex specific, age adjusted rates show steadily decreasing rates for males and a declining trend for females. The amount of reduction from 1970 to 1975 in Wisconsin is about what might be expected from observing the US white rates. (Graphs 3, 4, and 5)

C. The stomach cancer mortality age specific sex ratio for Wisconsin does not differ significantly from the US sex ratio. Stomach cancer mortality rates are about twice as high for males than as for females. (Graph 6)

D. Age adjusted stomach cancer mortality rates comparing the seven Wisconsin Health System Agency Areas reveal a similar pattern between the male and female rates. For both sexes HSA-7, HSA-6 and HSA-2 have the first, second and third highest rates respectively. Also, HSA-3 and HSA-1 have the lowest rates. This might be explained by geographical variations within Wisconsin of a stomach cancer risk factor that acts similarly for both sexes. (Graph 7)

E. Separately for each sex a multiplicative model proposed by Breslow and Day was fit to these data to estimate refined standardized mortality ratios for each Wisconsin county.

1) Goodness-of-fit tests for both the male and female model indicate there is no apparent reason to believe either model does not fit the data (males p = .39, females p = .60).

2) Tests for overall differences between the SMR estimates for the 72 counties indicate for both sexes, there is a statistically significant difference between counties, for males p = .0003 and for females p = .0019.
3) Wisconsin maps showing male and female SMR county estimates reveal a general pattern of higher mortality rates in the northern counties. (Maps 1 and 2) This seems to be consistent with what Mason et al.1 found regarding stomach cancer mortality between 1950 and 1969.

4) Two tests for geographical clustering of counties by SMR value were performed for each sex. The first considers the number of pairs of contiguous counties both with high (above the 50th percentile) SMR values. For males significantly more of such pairs of counties were found than what might be expected by chance alone (p = .024). For females, the number of such pairs was not significantly different than what might be expected.

The second test for geographical clustering considers the number of pairs of contiguous counties both with low (below the 50th percentile) SMR values. For both males and females the number of such pairs is not significantly different than what might be expected. However, the significance values are fairly small: p = .078 and p = .054, respectively.

II. DISCUSSION

In Wisconsin, cancer of the stomach ranks sixth among deaths due to cancer. Mortality rates from cancer of the stomach have precipitously decreased over the past forty years, when stomach cancer ranked first as the major site of deaths due to cancer. The five-year survival rate for this cancer is about 12 percent. The distribution stage at diagnosis among whites is approximately 18 percent local, 32 percent residual and 46 percent distant. Among blacks, a larger percentage of cases are diagnosed at later stages. No major advances in the treatment of stomach cancer have occurred since the 1930's when surgery became the treatment of choice. The vast majority of stomach cancer are of the carcinoma histologic type.

There are extreme differences in stomach cancer incidence and mortality between countries, adding credence to the theory that exogenous factors are heavily involved in the etiology of the disease. Native born Japanese, Chileans and Scandinavians have the highest rates of stomach cancer; Australia, New Zealand and the United States have the lowest rates. Migrant studies have shown that Polish-born Americans have an increased risk of stomach cancer and indicate that exposure to as yet unidentified factors would have occurred early in life.

In the United States, males have approximately twice the risk as females. Persons of lower socioeconomic status are also at higher risk but this relationship may be confounded by differences in dietary intake. Some familial aggregation is apparent.
A great deal of research on the etiology of stomach cancer in the past ten to fifteen years has concentrated on dietary factors. While some studies have been rather equivocal, intake of several types of foods have been positively associated with an increased risk of stomach cancer. These include heavily salted foods, fried and smoked foods, milk and milk products and diets heavy in starch, especially rice. Diets high in Vitamin C are negatively associated with increased stomach cancer risk. Some consideration has also been given as to the refrigeration of foods being associated with a reduced stomach cancer risk.

Occupations at high risk are iron, coal and slate miners, and building insulation, iron and asbestos workers. Frequent contact with soil and its organic materials and trace elements as well as with nitrate fertilizers and nitroso compounds have also been suggested as increasing the risk of stomach cancer.

Reviews on the epidemiology of stomach cancer can be found in the following:


MAP 2

STOMACH CANCER MORTALITY
FEMALE WISCONSIN RESIDENTS
1970-1975

SMR Estimate

[Map showing distribution of stomach cancer mortality rates among female Wisconsin residents from 1970 to 1975, with regions shaded to indicate significant top and low deciles, top half, and not significant.]
MALIGNANT NEOPLASMS OF THE STOMACH

* = WISC. MALE RATE (1970-1976)
△ = U.S. MALE RATE (1970)
DOTTED LINES INDICATE 95% C.I. FOR WISC. RATES
MALIGNANT NEOPLASMS OF THE STOMACH

GRAPH 2

\[ \text{* = WISC. FEMALE RATE (1970-1975)} \]
\[ \text{\triangle = U.S. FEMALE RATE (1970)} \]
\[ \text{DOTTED LINES INDICATE 95\% C.I. FOR WISC. RATES} \]

ANNUAL AGE SPECIFIC MORTALITY RATE PER 100,000

AGE
FEMALE STOMACH CANCER MORTALITY

**Indicate Wisconsin Rate**

**Indicate U.S. White Rate**

**Annual AgeAdjusted Mortality Rates Per 100,000**

- U.S. 1960 Standard

Data from Graph 28

MALIGNANT NEOPLASMS OF THE STOMACH

△ = WISC. MALE RATE
* = WISC. FEMALE RATE
DOTTED LINES INDICATE 95% C.I. FOR WISC. RATES

ANNUAL AGE ADJUSTED MORTALITY RATE PER 100,000

Directly Standardized to US 1970 Population
MALIGNANT NEOPLASMS OF THE STOMACH

* = WISC. RATIO (1970-1975)
\( \Delta \) = U.S. RATIO (1970)
DOTTED LINES INDICATE 95% C.I. FOR WISC. RATIO

MALE RATE / FEMALE RATE

AGE
MALIGNANT NEOPLASM OF STOMACH

\* = WISC. MALE RATE (1970-1975)
\( \Delta \) = WISC. FEMALE RATE (1970-1975)
BARS INDICATE 95% C.I. FOR WISC. RATES

DIRECTLY STANDARDIZED TO US
1970 POPULATION

ANNUAL AGE ADJUSTED MORTALITY RATE PER 100,000
I. RESULTS

A. No significant differences were found between US (1970) and Wisconsin (1970-1975) sex and age specific mortality rates for either colon cancer (ICDA 153.0-153.9) or rectal cancer (ICDA 154.0-154.2). For both colon and rectal cancer mortality there is a consistent rise in the rates with age.

B. The age adjusted US white mortality rates for male and female rectal cancer, as well as female colon cancer, have generally declined from 1935 to 1975. US white male colon cancer mortality has increased during this period. The annual sex specific colon and rectal cancer mortality rates in Wisconsin between 1970 and 1975 follow trends similar to those seen in the national rates.

C. No significant differences were found between US whites and Wisconsin age specific sex ratios. Overall the male and female ratio for rectal cancer mortality is higher than the corresponding ratio for colon cancer mortality. For both colon and rectal cancers, there is a male predominance.

D. The sex specific and age adjusted colon and rectal cancer mortality were determined for each of the seven Wisconsin Health System Agency areas (HSA's). For colon cancer all of the adjusted mortality rates are about equal, with the exception of the male rate for HSA-2. In this HSA, the Milwaukee area, the male rate is statistically significantly higher than the corresponding female rate. The male rate for HSA-2 is higher than the male rate for the other HSA areas although this difference is not statistically significant.

Rectal cancer mortality by HSA areas shows female rates consistently lower than corresponding male rates. There do not appear to be large differences between the geographical areas. However, the HSA areas with relatively high male rates also have relatively high female rates. The same relation holds for areas with relatively low mortality. If these differences in rectal cancer mortality rates are an actual reflection of differences in the occurrence of rectal cancer, it would indicate the presence of an etiologic agent(s) that: a) has significant variation between geographical areas within Wisconsin, and b) acts in a similar manner for both males and females.

E. The multiplicative model proposed by Breslow and Day was fit to the data in order to obtain estimates for revised standardized mortality ratios for each county. Separate models were fit for male and female, colon and rectal cancer mortality data.
1. A goodness-of-fit test for each model was performed. The results indicate that there is no reason to believe the models do not fit the data. The significance values for site and sex are as follows: male rectal cancer $p = .80$, female rectal cancer $p = .49$, male colon cancer $p = .06$, female colon cancer $p = .80$. Note that the value for male colon cancer is fairly small indicating a possibility of lack-of-fit, however this is still not significant.

2. For each site and sex a test for an overall difference between the 72 counties was performed. The male and female rectal cancer SMR estimates show significant overall differences between counties, $p = .0025$ and $p = .00005$, respectively. The male colon cancer SMR estimates also have a significant overall difference, $p = .0003$. No overall differences between county SMR estimates for female colon cancer were found, $p = .156$.

3. Maps of Wisconsin were generated indicating the SMR estimates for each county as well as those counties significantly different from the remainder of the state. For male and female colon cancers and male rectal cancer no discernable patterns of counties with high or low SMR estimates are seen. For female rectal cancer a large block of counties in the north central part of the state has higher SMR estimates than the surrounding areas.

4. Tests for geographical clustering of counties by SMR estimates reveal that for female rectal cancer mortality the number of pairs of contiguous counties both with high SMR estimates is larger than what might be expected from chance, $p = .01$. For male rectal cancer as well as male and female colon cancer, no significant geographical clusters of counties were found. Similar tests looking for clusters of counties with low SMR estimates revealed no significant results in all cases.

II. DISCUSSION

Colorectal cancers are among the most common forms of cancer in western societies. It has been estimated that in western populations from 9 to 19 percent of all cancer deaths are attributed to colorectal cancer. These figures translate into from two to four percent of the deaths from all causes combined.

Anatomical and histological distribution of colorectal malignancies within the United States can be examined from the Third National Cancer Survey (TNCS). Almost 70 percent of the cancers of the large intestine were located in the colon. The majority of the rest developed in the rectosigmoid junction followed by the rectum. For tumors of the colon, the largest number were located in the sigmoid. The vast majority of the histologically confirmed cancers of the large intestine were classified as adenocarcinomas. The histological type did not vary strikingly with the location of the tumor in the intestine.
There is a great deal of variation in colorectal cancer rates between countries. Generally higher rates are experienced in the highly developed or westernized countries. Low rates are evident in the primitive or developing countries. Colon cancer incidences can range from 1.3 cases per 100,000 person-years in Ibadan, Nigeria, to 30 per 100,000 in Connecticut. The corresponding rectal cancer incidence rates are 1.2 and 18.2, respectively. Generally, colon cancer and rectal cancer rates are positively correlated. However, the range of the rectal cancer incidence rates is not as great as that of colon cancer. Consequently, the proportion of rectal cancer cases to colon cancer cases is high for those countries with low rates.

Within the United States the overall mortality rates for colon cancer have remained nearly stable for the past 30 years. However, this may be misleading since the male mortality rates have been increasing while the female rates have been decreasing over this period. The US rectal cancer mortality rates have been decreasing for both sexes. Incidence data from the Connecticut Tumor Registry indicates an increase in the occurrence of colon cancer for both males and females. However, since 1950 the increases for female colon cancer incidence have been small. The rectal cancer incidence in Connecticut seems to be nearly stable from 1940 through 1973.

In the United States there is a steady and rapid increase in colorectal cancer rates with each five-year age group up to the final age group over 85 years old. For this particular age group, 85+, incomplete ascertainment of cases is possibly a major problem. Colorectal cancer is very rare among persons under 20. In these unusual cases, the histologic classification and the location of the tumor tends to be different from what is observed in the older population. Often tumors in young persons are associated with identifiable, predisposing factors such as familial polyposis, ulcerative colitis, or being a member of a "cancer family."

Migrant studies have suggested that environmental factors may play an important role in determination of colorectal cancer risk. These studies indicate that the colorectal cancer rates for different racial groups living in the same geographical area tend to converge over time. Furthermore, migrating populations tend to assume the colorectal cancer rates specific to the host population and it appears that the migrating population's rates change relatively quickly. This suggests an environmental influence that can operate after a relatively short exposure as well as can operate throughout one's life span.

Dietary intake has been implicated as being the predominant environmental factor associated with colorectal cancer causation. Diet composition between high and low risk populations has been compared. Increased consumption of animal fat and foods of animal origin coupled with the decreased consumption of fiber and foods of vegetable origin has been associated with countries with increased colon cancer rates. Biological mechanisms by which low-fiber diets and/or high animal fat diets may cause colonic cancer have been proposed. Further work is needed before the actual mechanism linking colorectal cancer and diet can be established.
The fiber hypothesis maintains that increased amounts of fiber in the diet lessen the opportunity for carcinogenesis from luminal factors. This is accomplished by decreased transit time of material through the intestines as well as increasing the total bulk content. Decreased transit time may reduce the opportunity for bacteria to produce a carcinogen as well as lessens the time a carcinogen may be in contact with the stomach wall. Increased bulk is thought to dilute carcinogenic material.

The high-fat hypothesis suggests that such a diet increases neutral sterols and bile acids in the bowel. Furthermore, such a diet modifies bacterial enzymatic activity. The combination results in the production of a carcinogen.

Further work is needed before one or both of these theories is shown to be correct.

Reviews on the epidemiology of colo-rectal cancer can be found in the following:


MALIGNANT NEOPLASMS OF THE COLON

Graph 1

* = WISC. MALE RATE (1970-1975)
△ = U.S. MALE RATE (1970)
DOTTED LINES INDICATE 95% C.I. FOR WISC. RATES

ANNUAL AGE SPECIFIC MORTALITY RATE PER 100,000

10^6
10^5
10^4
10^3
10^2
10^1
10^{-1}
10^{-2}

0. 10. 20. 30. 40. 50. 60. 70. 80. 90.

AGE
MALIGNANT NEOPLASMS OF THE COLON

* = WISC. FEMALE RATE (1970-1975)
△ = U.S. FEMALE RATE (1970)
DOTTED LINES INDICATE 95% C.I. FOR WISC. RATES

ANNUAL AGE SPECIFIC MORTALITY RATE PER 100,000

AGE
MALIGNANT NEOPLASMS OF THE RECTUM

* = WISC. MALE RATE (1970-1975)
△ = U.S. MALE RATE (1970)
DOTTED LINES INDICATE 95% C.I. FOR WISC. RATES

ANNUAL AGE SPECIFIC MORTALITY RATE PER 100,000

10^5
10^4
10^3
10^2
10
10^-1
10^-2

0.  10.  20.  30.  40.  50.  60.  70.  80.  90.

AGE
MALIGNANT NEOPLASMS OF THE RECTUM

$\star$ = WISC. FEMALE RATE (1970-1975)
$\triangle$ = U.S. FEMALE RATE (1970)
Dotted lines indicate 95% C.I. for WISC. rates

ANNUAL AGE SPECIFIC MORTALITY RATE PER 100,000

$10^5$

$10^4$

$10^3$

$10^2$

$10^1$

$10^0$

$10^{-1}$

$10^{-2}$

0. 10. 20. 30. 40. 50. 60. 70. 80. 90.

AGE
MALE COLON CANCER MORTALITY

- INDICATE U.S. WHITE RATE

* INDICATE WISCONSIN RATE

ANNUAL AGE ADJUSTED MORTALITY RATES PER 100,000

0.  2.  4.  6.  8.  10.  12.  14.  16.

U.S. 1950 STANDARD

MALE RECTAL CANCER MORTALITY

ANNUAL AGE ADJUSTED MORTALITY RATES PER 100,000

* INDICATE WISCONSIN RATE
△ INDICATE U.S. WHITE RATE

* U.S. 1950 STANDARD

FEMALE RECTAL CANCER MORTALITY

**INDICATE WISCONSIN RATE**
**△ INDICATE U.S. WHITE RATE**

**ANNUAL AGE ADJUSTED MORTALITY RATES PER 100,000**

U.S. 1960 STANDARD
MALIGNANT NEOPLASMS OF THE COLON

△ = WISC. MALE RATE
★ = WISC. FEMALE RATE
DOTTED LINES INDICATE 95% C.I. FOR WISC. RATES

ANNUAL AGE ADJUSTED MORTALITY RATE PER 100,000

Directly Standardized to US 1970 Population

MALIGNANT NEOPLASMS OF THE RECTUM

\[ \Delta = \text{WISC. MALE RATE} \]
\[ \ast = \text{WISC. FEMALE RATE} \]
Dotted lines indicate 95% C.I. for WISC. rates

ANNUAL AGE ADJUSTED MORTALITY RATE PER 100,000

Directly Standardized to US
1970 Population

MALIGNANT NEOPLASMS OF THE COLON

* = WISC. RATIO (1970-1975)
△ = U.S. RATIO (1970)
DOTTED LINES INDICATE 95% C.I. FOR WISC. RATIO

MALE RATE / FEMALE RATE

AGE
MALIGNANT NEOPLASMS OF THE RECTUM

* = WISC. RATIO (1970-1975)
△ = U.S. RATIO (1970)
DOTTED LINES INDICATE 95% C.I. FOR WISC. RATIO

MALE RATE / FEMALE RATE

AGE
**MALIGNANT NEOPLASMS OF THE COLON**

- ▲ = WISC. FEMALE RATE (1970-1975)
- BARS INDICATE 95% C.I. FOR WISC. RATES

**ANNUAL ADJUSTED MORTALITY RATE PER 100,000**

Directly Standardized to US 1970 Population
MALIGNANT NEOPLASM OF RECTUM

* = WISC. MALE RATE (1970-1975)
▲ = WISC. FEMALE RATE (1970-1975)
BARS INDICATE 95% C.I. FOR WISC. RATES

ANNUAL AGE ADJUSTED MORTALITY RATE PER 100,000

Directly Standardized to US 1970 Population
PANCREATIC CANCER MORTALITY IN WISCONSIN
1970-1975
ICDA 157.0-157.9

I. RESULTS

A. Wisconsin age and sex specific pancreatic cancer mortality rates are not statistically significantly different from those for the entire United States. (Graphs 1 and 2)

B. Between 1930 and 1970, the US white age adjusted mortality rates have increased consistently for both sexes. This may be a result of improved diagnostic procedures. The 1973-1974 US white rates are not higher than the 1969-1971 mortality rates. Annual age adjusted Wisconsin pancreatic cancer mortality rates between 1970 and 1975 also do not show any significant increases. (Graphs 3, 4, and 5)

C. Comparisons between the US and Wisconsin age specific sex ratios do not indicate any significant differences. (Graph 6)

D. Furthermore, no differences were found between the age adjusted mortality rates of the seven Wisconsin Health System Agency Areas of the state. (Graph 7)

E. A multiplicative model was fit to the pancreatic cancer mortality data to estimate county SMR values:

1. For both sexes a goodness-of-fit test for the model showed no apparent lack of fit (females p = .21, males p = .46).

2. For females a test for an overall difference between county SMR estimates showed no significant differences, p = .41. A similar test for male pancreatic cancer SMR estimates did indicate a difference between-counties, p = .003.

3. Maps of the county SMR estimates for each sex did not reveal any obvious geographical patterns. (Maps 1 and 2)

4. Tests for geographical clustering of high, and low, SMR values did not indicate geographical clustering for either sex.

II. DISCUSSION

In the United States, pancreatic cancer is a major cause of death. It is the fourth leading cause of death among all sites of cancer. Pancreatic cancer incidence rates are increasing. The rate of increase is faster than all other cancers excluding lung cancer. The prognosis for this disease is extremely poor; one-year survival is about ten percent, five-year survival is about two percent. The majority of pancreatic cancer patients have metastatic spread
at the time of laparotomy (abdominal section). The reason for this is that pancreatic cancer is difficult to diagnose. Vague and nonspecific physical symptoms, the placement of the pancreas in proximity to important blood vessels and vital organs, and person-to-person variation of exact size and location within the body, are the major factors for the difficulty in diagnosis.

Very little is known concerning the etiology of this cancer. Incidence and mortality rates show men are perhaps twice as likely to develop the disease. There is a tremendous increase in pancreatic cancer rates with age. In the United States, blacks seem to have a higher risk than whites, however this is probably confounded with diagnostic factors such as socioeconomic status. Internationally, Americans have higher rates than Europeans, and Europeans have higher rates than Japanese and Isrealis. Time trends indicate that the increase in mortality rates are generally about the same magnitude. The Japanese rates are increasing most rapidly. This has lead to suggestions of dietary or environmental factors.

Other suspected risk factors include cigarette smoking and occupation. A number of studies have consistently shown increased pancreatic mortality for cigarette smokers versus nonsmokers. There are conflicting results as to whether or not this risk increases with the number of cigarettes smoked per day. Regardless, this association is not as strong as that seen between lung cancer and cigarette smoking.

High mortality rates for this disease have been seen for workers of coke and gas plants, as well as for workers exposed to benzidine and/or betanaphthylamine. One study has found significantly higher pancreatic cancer mortality for members of the American Chemical Society. Also workers in heavy metal industries may have increased risks. The increasing number of workers exposed to various chemicals may be a major factor in explaining the rising incidence rates for this cancer.

It is not clear how these and other suspected risk factors might relate to the particular geographical and secular patterns of pancreatic cancer mortality seen in Wisconsin.

Reviews of the epidemiology of pancreatic cancer can be found in the following:


MALIGNANT NEOPLASMS OF THE PANCREAS

* = WISC. FEMALE RATE (1970-1975)
△ = U.S. FEMALE RATE (1970)
DOTTED LINES INDICATE 95% C.I. FOR WISC. RATES

ANNUAL AGE SPECIFIC MORTALITY RATE PER 100,000

0.  10.  20.  30.  40.  50.  60.  70.  80.  90.

AGE
ANNUAL AGE SPECIFIC MORTALITY RATE PER 100,000

MALIGNANT NEOPLASMS OF THE PANCREAS

\[ * = \text{HIS} \cdot \text{C. MALE RATE (1970-1975)} \]
\[ \triangle = \text{U.S. MALE RATE (1970-1975)} \]
\[ \text{DOTTED LINES INDICATE 95\% C.I. FOR HIS. RATES} \]

GRAPH 1
MALE PANCREATIC CANCER MORTALITY

* INDICATE WISCONSIN RATE
△ INDICATE U.S. WHITE RATE

ANNUAL AGE ADJUSTED MORTALITY RATES PER 100,000

* U.S. 1950 STANDARD

MALIGNANT NEOPLASMS OF THE PANCREAS

\[ \Delta = \text{WISC. MALE RATE} \]
\[ \star = \text{WISC. FEMALE RATE} \]

DOTTED LINES INDICATE 95% C.I. FOR WISC. RATES

DIRECTLY STANDARDIZED TO US
1970 POPULATION

ANNUAL AGE ADJUSTED MORTALITY RATE PER 100,000

MALIGNANT NEOPLASMS OF THE PANCREAS

* = WISC. RATIO (1970-1975)
▲ = U.S. RATIO (1970)
DOTTED LINES INDICATE 95% C.I. FOR WISC. RATIO

MALE RATE / FEMALE RATE

AGE
MALIGNANT NEOPLASM OF PANCREAS

* = WISC. MALE RATE (1970-1975)
▲ = WISC. FEMALE RATE (1970-1975)
Bars indicate 95% C.I. for WISC. rates

ANNUAL AGE ADJUSTED MORTALITY RATE PER 100,000

Directly Standardized to US
1970 Population
LUNG CANCER MORTALITY IN WISCONSIN
1970-1975
ICDA 162.0-162.1

I. RESULTS

A. Sex and age specific lung cancer mortality rates for Wisconsin during 1970-1975 are generally slightly lower than corresponding rates for the US in 1970. Wisconsin rates are consistently lower than the US rates for both males and females over 35 years of age. However, the general shape of both the male and female age specific curves for Wisconsin are very similar to the corresponding curves for the entire US. (Graphs 1 and 2)

The county lung cancer mortality maps for 1950-1969 show Wisconsin as having on the most part significantly lower rates than the rest of the US. This is consistent with the comparisons between Wisconsin and the US.

B. Both male and female lung cancer mortality show dramatic increases. The US male lung cancer mortality has been steadily increasing throughout the 1935-1975 time period. The Wisconsin male lung cancer rates show a significant increase between 1970 and 1975. This increase is about the same magnitude as what is seen in the national rates.

The US female lung cancer rates show a dramatic rise after 1960. This increase might be attributed to the rise in the percentage of women smoking cigarettes twenty years previous. The 1970 to 1975 Wisconsin female lung cancer mortality rates also show increases of the same order of magnitude as those seen in the national rates.

C. The lung cancer mortality age specific sex ratios for Wisconsin do not differ significantly from those of the US. There is a peak in the sex ratio between the ages of 65 and 80 where the male rate is about seven times the female rate.

D. Comparisons of male age adjusted rates by Health Systems Agency Areas show a significantly higher rate for HSA-2, the Milwaukee area. HSA-1, the southwestern part of the state, may also have a higher male lung cancer mortality rate. The rates for females seems to be fairly consistent from one HSA to the next. (Graph 7)

E. A multiplicative model was fit to both the male and female lung cancer data to estimate refined sex specific standardized mortality ratio SMR's for each county in Wisconsin.
1. Goodness-of-fit tests for both the male and female models indicate no apparent reason to believe the models do not fit the data adequately, males $p = .13$, females $p = .89$.

2. Tests for an overall difference in county SMR estimates indicate that for males there is a highly significant overall difference ($p < 10^{-6}$). For females there is a nonsignificant overall difference in county SMR estimates ($p = .061$). This significance value is fairly small, however.

3. A Wisconsin map showing male lung cancer SMR estimates indicates that counties in the extreme southeastern part of the state have significantly higher male lung cancer mortality. An area in the middle part of the state seems to have significantly lower male lung cancer mortality. (Map 1) The corresponding map for female lung cancer mortality shows high SMR estimates in some of the same southeastern counties: Kenosha, Milwaukee and Walworth, but the pattern is not as strong.

4. Tests for geographical clustering of counties based on the SMR estimates were performed for both males and females; the number of pairs of contiguous counties with high (upper 50th percentile) SMR estimates is not significantly different from what might be expected due to chance. For females the number of pairs of counties with low (lower 50th percentile) SMR estimates is also not significant. For males, the number of pairs of counties with low SMR estimates is nearly significant ($p = .054$).

II. DISCUSSION

Lung cancer is currently the second leading cause of death in the United States. Both the incidence and mortality rates for this disease have been increasing. This increase is seen in both the white and nonwhite rates for males and females. Among all cancers, lung cancer incidence is increasing most rapidly. Furthermore, for white males in the United States the incidence of all other cancers, excluding lung cancer, is dropping.

Lung cancer is unique with respect to most human cancers in that the major cause is known and is preventable. The evidence of cigarette smoking as being a primary cause of lung cancer comes from four major sources.

First, a dose-response relationship has been found between number of cigarettes smoked and risk of lung cancer. Retrospective as well as prospective epidemiological studies have shown this relationship.

Second, the demographic distribution of populations with high and low lung cancer risk have been shown to correspond to long-term smoking habits. Examples demonstrating this relationship are studies comparing time trends in male and female smoking habits and lung cancer mortality rates. Studies have also examined lung cancer rates in populations with unusual smoking habits such as the Seventh Day Adventists.
Third, studies have shown reduced lung cancer risk among exsmokers. In England and Wales, one study examined the lung cancer experience of a large number of medical doctors who quit smoking.* More recently other epidemiological studies support this conclusion.

Fourth, cancer has been produced in a number of animal species by either inhalation of cigarette smoke or exposure to tars and other carcinogens present in cigarette smoke.

The fact that cigarette smoking is a cause of lung cancer does not preclude the concept that this disease has multifactorial causes. There is some evidence that the genetic constitution of an individual may influence lung cancer risk. Certain chemicals in the environment are also believed to be able to cause lung cancer. In many cases these chemicals are thought to interact synergistically with cigarette smoke. An example of such a chemical is asbestos. Exposure to asbestos considerably increases lung cancer risk among smokers. Among nonsmokers exposed to asbestos, the increase is not nearly as high. Some other chemicals in the environment that are suspected of being linked with lung cancer are inorganic arsenic, nickel, chromium, iron ore (hematite), vinyl chloride, halo ethers and polycyclic aromatic hydrocarbons. Radiation may also play an important role in lung cancer causation.

Higher lung cancer mortality rates have been observed among urban populations compared to rural populations. Also higher rates are seen for low socioeconomic status populations. Nutritional factors have been proposed as an explanation for these differences. However, the specific factors and mechanisms involved are not clear. Environmental pollution has also been suggested to explain these gradients in lung cancer mortality.

Reviews on the etiology of lung cancer can be found in the following:


MALIGNANT NEOPLASMS OF TRACHEA, BRONCHUS, AND LUNG

GRAPH 1

\( * = \text{WISC. MALE RATE (1970-1975)} \)
\( \triangle = \text{U.S. MALE RATE (1970)} \)

DOTTED LINES INDICATE 95% C.I. FOR WISC. RATES

ANNUAL AGE SPECIFIC MORTALITY RATE PER 100,000

\( 10^5 \)
\( 10^4 \)
\( 10^3 \)
\( 10^2 \)
\( 10 \)
\( 1 \)
\( 10^{-1} \)
\( 10^{-2} \)

AGE

0, 10, 20, 30, 40, 50, 60, 70, 80, 90.
MALE LUNG CANCER MORTALITY

- W INDICATE WISCONSIN RATE
- ▲ INDICATE U.S. WHITE RATE

ANNUAL AGE ADJUSTED MORTALITY RATES PER 100,000

* U.S. 1850 STANDARD


GRAPH 3
Graph 5

Annual Age Adjusted Mortality Rate per 100,000

- ▲ = WISC. MALE RATE
- ★ = WISC. FEMALE RATE

Dotted lines indicate 95% C.I. for WISC. rates

Directly Standardized to US 1970 Population
MALIGNANT NEOPLASMS OF TRACHEA, BRONCHUS, AND LUNG

\* = WISC. RATIO (1970-1975)
\^ = U.S. RATIO (1970)
DOTTED LINES INDICATE 95% C.I. FOR WISC. RATIO

MALE RATE / FEMALE RATE

AGE
MALIGNANT NEOPLASM OF THE TRACHEA, BRONCHUS, AND LUNG

GRAPH 7

* = WISC. MALE RATE (1970-1975)
\(\Delta\) = WISC. FEMALE RATE (1970-1975)
BARS INDICATE 95\% C.I. FOR WISC. RATES

ANNUAL AGE ADJUSTED MORTALITY RATE PER 100,000

Directly Standardized to US 1970 Population
FEMALE BREAST CANCER MORTALITY IN WISCONSIN
1970-1975
ICDA 174.0-174.9

I. RESULTS

A. Age specific female breast cancer mortality rates in Wisconsin during this period are very similar to those for the US in 1970. (Graph 1)

B. Secular trends of age adjusted mortality rates for the white US population remained fairly constant between 1935 and 1975. The corresponding rates for Wisconsin between 1970 and 1975 reveal no important differences. (Graph 2) Wisconsin age adjusted mortality rates do not show any statistically significant secular trends over this period. (Graph 3)

C. Comparisons of age adjusted mortality rates between the seven Wisconsin Health System Agency Areas (HSA's) indicate HSA-2, the Milwaukee area, may have slightly higher rates. (Graph 4) However, this is not a statistically significant difference.

D. A multiplicative model proposed by Breslow and Day was fit to these data to estimate a refined standardization mortality ratio (SMR) for each county.

1. A goodness-of-fit test for the model indicates that there is no apparent reason to believe the model does not fit the data, p = .49.

2. A test of an overall difference between the SMR estimates for the 72 Wisconsin counties indicates there is no statistically significant difference between counties. However, the significance value is fairly small, p = .078.

3. A test for a difference in SMR estimates between Milwaukee County and the rest of the state taken as a whole indicates that Milwaukee county has a significantly higher rate, p = .000002. This is consistent with mortality data from 1950 to 1969 analyzed by Mason et al. indicating Milwaukee county as having significantly higher breast cancer mortality compared to the US.

4. The Wisconsin map showing the SMR estimates shows no obvious geographical pattern of high and low rates. (Map 1) This, too, is consistent with Mason et al.
5. Two tests for geographical clustering of counties by SMR values were performed. The first considers the number of pairs of contiguous counties with high (above the 50th percentile) SMR estimates. The second considers the number of pairs of contiguous counties with low (below the 50th percentile) SMR estimates. In both cases the results show nothing different than what might be expected from chance.

II. DISCUSSION

Among the major cancers in western countries, the epidemiology of breast cancer has undergone the most study. Thus, numerous predictors of risk have been described and refined.

The risk factors for breast cancer can be divided into four general categories: demographic, exogenous, endogenous ovarian and endogenous nonovarian.

Commonly cited demographic risk factors include: socioeconomic status, age, race, marital status and being Jewish. Each of these however is subject to variability depending on the setting, and confounding by other factors: the relatively constant age incidence of breast cancer in Oriental populations disappears in two generations after immigration to a western country; the effect of marital status is dependent on the more fundamental biologic effects of age at first birth/parity.

Exogenous rate factors of interest in recent studies include viruses, oral contraceptives, estrogen, reserpine and radiation. With the exception of ionizing radiation in substantial doses (atomic bomb survivors), none of these appear to be well established in current studies.

Endogenous ovarian risk factors include early menarche, late menopause, late first birth and nulliparity. These all share relatively low relative risks (two- to three-fold) but have been consistently demonstrated in different populations.

Endogenous nonovarian risk factors include a family history of breast cancer, obesity, and benign breast disease.

In general, a family history of breast cancer increases risk two- to three-fold, but certain relatively rare patterns of breast cancer in families may increase risk as much as ten-fold. Obesity as a risk factor for breast cancer appears inconsistent, and if valid, is limited to postmenopausal women. Benign breast disease appears to be a risk factor but its relative risk is variable depending on the definition of benign breast disease.

The suggestion of a higher breast cancer mortality in an urban county, Milwaukee, compared to the state might be due to an uneven distribution of risk factors based on rural/urban differences. Increased socioeconomic status and increased age at first pregnancy, both likely in a more urban setting, would increase the breast cancer risk of such a population. Other known and unknown
Risk factors might play a role. Investigation of risk factors in this population would be needed to address this question.

Recent reviews of the epidemiology of breast cancer can be found in the following:


MALIGNANT NEOPLASM OF BREAST

GRAPH 1

* = WISC. FEMALE RATE (1970-1975)
△ = U.S. FEMALE RATE (1970)
DOTTED LINES INDICATE 95% C.I. FOR WISC. RATES

ANNUAL AGE SPECIFIC MORTALITY RATE PER 100,000

10^5

10^4

10^3

10^2

10^1

10^0

10^-1

10^-2

0.  10.  20.  30.  40.  50.  60.  70.  80.  90.

AGE
MALIGNANT NEOPLASM OF BREAST

* = WISC. MALE RATE
△ = WISC. FEMALE RATE
DOTTED LINES INDICATE 95% C.I. FOR WISC. RATES

ANNUAL ADJUSTED MORTALITY RATE PER 100,000

Directly Standardized to US
1970 Population

MALIGNANT NEOPLASM OF BREAST

\* = WISC. MALE RATE (1970-1975)
\^ = WISC. FEMALE RATE (1970-1975)
BARS INDICATE 95% C.I. FOR WISC. RATES

DIRECTLY STANDARDIZED TO US
1970 POPULATION

ANNUAL AGED ADJUSTED MORTALITY RATE PER 100,000
CERVICAL CANCER MORTALITY IN WISCONSIN
1970-1975
ICDA 180.0-180.9

I. RESULTS

A. Wisconsin age specific cervical cancer mortality rates for 1970-1975 are significantly lower than the 1970 US rates for the age groups 25 through 75. Since the cervical cancer mortality rates have been rapidly decreasing, the 1970-1975 Wisconsin rates were also compared to the US 1975 rates. Also Wisconsin rates were compared to the US white rates since Wisconsin is predominantly white and there appears to be a greater cervical cancer risk for blacks compared to whites. In all cases the Wisconsin cervical cancer mortality rates remain significantly below the national rates. (Graph 1)

B. Age adjusted cervical cancer mortality rates for US whites show a dramatic decline over the period from 1950 to 1970. The corresponding Wisconsin rates from 1970 to 1975 also show a downward trend; however, because of the relatively low mortality rate and short time period, this decline was not statistically significant.

C. Comparisons in cervical cancer mortality within Wisconsin reveal little difference in the age adjusted rates among the seven Health System Agency Areas.

D. The multiplicative model proposed by Breslow and Day was fit to the cervical cancer mortality data to obtain county revised standardized mortality ratio estimates for each county.

1. The results of a goodness-of-fit test indicate no reason to believe this model does not adequately describe the data; however, the significance level is relatively small, p = .08.

2. A statistical test for determining if significant overall differences exist among the 72 county SMR estimates indicates these differences are present, p = .0003.

3. A Wisconsin map indicating the cervical cancer county SMR estimates reveals low values for a large group of counties in the center of the state. A band of counties with high SMR's exists along the northern border of the state. Three smaller clusters of counties with high SMR estimates is present near Trempealeau, Adams, and Rock counties.
4. A test for geographical clustering of counties indicates a statistically significant clustering of counties with low cervical cancer SMR estimates. The number of pairs of contiguous counties both with low SMR estimates is larger than what might be expected from chance alone, \( p = .002 \). The corresponding test for pairs of contiguous counties with high SMR estimates revealed no significant geographical clustering.

II. DISCUSSION

Currently in the United States, the age adjusted mortality rate for cervical cancer is significantly below what it was in 1950. The quality of the cervical cancer mortality data would tend to underestimate the magnitude of the cervical cancer rates in earlier time periods. As late as 1966 over one-quarter of all uterine cancers were classified as "other and unspecified." Many of these were undoubtedly cervical cancer hence not counted in the cervical cancer rate. The improvements in relative survival are too small to explain the decline in cervical cancer mortality.

One factor that may cause some difficulty when interpreting these changes in rates is the increasing number of hysterectomies performed throughout this period. This would have the effect of decreasing the cervical cancer rate since fewer women in the population would be at risk.

Age adjusted cervical cancer incidence has doubled for both whites and nonwhites since 1950. This increase in incidence is a result of an increase of \textit{in situ} cervical cancers. \textit{In situ} cervical cancer accounts for over one-half of all cervical cancers in women under age 45. This increase has been largely attributed to cytological screening and early diagnosis. However, effects of increased sexual promiscuity, a suspected risk factor, cannot be ignored.

Among older women the cervical cancer incidence rates have decreased since 1950. These cancers are primarily the invasive type. Over one-half of the cervical cancers of women over 50 years of age are invasive. Furthermore, the rate for young women with invasive cervical cancer also seems to be declining.

In the United States, incidence of invasive cervical cancer is about twice as high for blacks compared to whites. For \textit{in situ} cervical cancer incidence rates vary widely among both blacks and whites within the US. This variation may be a result of differentials in diagnostic procedures, as well as cytological screening.

The natural history of cervical cancer is largely unresolved. Whether cervical dysplasia develops into cervical carcinoma is not known. Some evidence suggests that the more severe dysplasias are more likely to progress to carcinomas. Another area where more work needs to be done concerns whether cervical cancer \textit{in situ} progresses to invasive carcinoma. Probably a high proportion of \textit{in situ} lesions eventually progress to invasive disease; however, some evidence indicates
this is not always the case. Some of the problems involved in demonstrating a relationship between cervical dysplasia and the various types of cervical carcinoma involve the precise definitions of the terms involved. Also there is a problem of the length of time a woman with cervical dysplasia or in situ carcinoma may be followed without some sort of intervention.

Cancer of the uterine cervix appears to occur excessively among women with high levels of sexual exposure, especially when initiated in adolescence. A current etiological hypothesis concerning this cancer involves a carcinogenic agent transmitted by the coital male to the female at risk. One suggested transmissible agent is a herpes simplex type two virus (HSV-2). This suggestion is derived mainly from two types of data. First, several epidemiological studies have generally found an increase in antibodies to HSV-2 among women with cervical cancer compared to various types of control groups. Second, studies of these antigens in cancer tissue as well as tests for herpes virus generated within the tumor are providing support for the presence of this virus in cervical cancer. The relation between this virus and dysplasia, carcinoma in situ, and invasive carcinoma is not known. It seems reasonable to conclude that HSV-2 may be a necessary factor for cervical cancer. However, since this virus is much more prevalent than cervical cancer disease, it is probably most often a benign sequel of sexual intercourse.

The suggestion has been made that circumcision may have a protective effect regarding penile as well as cervical carcinomas. Jews and Fijians who practice circumcision have low rates for both of these cancers. A study by Wynder, et al, showed an increased relative incidence of cervical cancer among blacks. These blacks had a near absence of circumcised sexual partners. However, to date there is little evidence that demonstrates an effect of circumcision on cervical cancer. The same can be said for the suspected carcinogenic role of smegma.

Reviews of the epidemiology of cervical cancer can be found in the following articles:


ANNUAL AGE SPECIFIC MORTALITY RATE PER 100,000

CERVICAL CANCER MORTALITY

Graph 1

\[ \frac{12}{13} = \text{MISC. FEMALE RATE (1970-1975)} \]
\[ \Delta = \text{U.S. FEMALE RATE (1970)} \]
\[ \text{DOTTED LINES INDICATE 95\% C.I. FOR MISC. RATES} \]
CERVICAL CANCER MORTALITY

GRAPH 3

\[ \Delta = \text{WISC. FEMALE RATE} \]
\[ \text{DOTTED LINES INDICATE 95\% C.I. FOR WISC. RATES} \]

ANNUAL AGE ADJUSTED MORTALITY RATE PER 100,000

Directly Standardized to US 1970 Population
CERVICAL CANCER MORTALITY

\[ \Delta = \text{WISC. FEMALE RATE (1970-1975)} \]

BARS INDICATE 95% C.I. FOR WISC. RATES

DIRECTLY STANDARDIZED TO US 1970 POPULATION

ANNUAL AGE ADJUSTED MORTALITY RATE PER 100,000
CORPUS UTERI CANCER MORTALITY IN WISCONSIN
1970-1975
ICDA 182.0-182.9

I. RESULTS

A. Age specific mortality rates for corpus uteri cancer do not indicate any significant differences between Wisconsin and the US. In both cases there is a rapid and progressive rise in the rates with age. (Graph 1)

B. There is a marked reduction in the age adjusted white US corpus uteri mortality rate between 1950 and 1975. The Wisconsin rates are comparable to the US white rates. (Graph 2) However, there is not any significant reduction in the Wisconsin mortality rates between 1970 and 1975. (Graph 3)

C. Comparisons of the annual age adjusted mortality rates by Health System Agency Area reveal no significant differences. (Graph 4)

D. A multiplicative model proposed by Breslow and Day was fit to these data to estimate a revised standardized mortality ratio for each county.

1. A goodness-of-fit test for this model indicates that there is no apparent reason to believe the model does not fit the data, $p = .31$.

2. A test of an overall difference between county SMR estimates indicates a statistically significant difference, $p = .005$.

3. A map of Wisconsin showing the SMR estimates for each county as well as indicating which counties are statistically significantly different from the rest of the state ($p < .05$) reveals no obvious patterns. The 1950-1969 corpus uteri cancer mortality data from Mason et al.\(^1\) shows no geographical patterns in Wisconsin.

4. Tests for geographical clustering of counties by SMR value were performed. The first test considers the number of pairs of contiguous counties both with high (upper 50th percentile) SMR estimates. This number was found to be no different than what might be expected from chance, $p = .33$.

The second test considers the number of pairs of contiguous counties both with low (lower 50th percentile) SMR estimates. This number was also not significantly different than what might be expected from chance; however, the significance level is fairly small, $p = .08$. 

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II. DISCUSSION

Among invasive cancers of the white female genital organs, the corpus, or body of the uterus, presently has the highest incident rate in the US. For black US women, this rate is second to cervical cancers.

Studies based on death certificates show a striking decrease in US endometrial cancer mortality over the past quarter century for both whites and blacks. Because of the changes in the quality and classification schemes of the mortality data, the exact amount of these decreases in endometrial cancer mortality is not known. However, it is generally accepted that the mortality rates from this cancer have decreased substantially. A comparison of incidence rates from the Second (1947-48) and Third (1969-71) Cancer Surveys show a decline among black US women but not among the white female population. There is some recent evidence to suggest an increase in endometrial cancer incidence but this remains equivocal at this time.

World-wide comparison of incidence rates show American whites as having the highest rates while women in Asian countries tended to have the lowest rates. The patterns seen in endometrial cancer are generally similar to those seen in breast or ovarian cancer.

Migrant studies concerning American-born Japanese have shown a shifting of breast cancer rates from the lower Japanese rates toward the American rates. This observation has not yet been observed for endometrial cancer incidence; however, at the present time there may be too few endometrial cancer cases to enable the calculation of an accurate endometrial cancer rate.

The mortality rates for US nonwhites are about double those for whites. However, the nonwhite incidence rates are about half those of the whites. Among nonwhites, a greater percentage of corpus cancers are either sarcomas or mixed cell histology compared to whites, 21 percent versus six percent, respectively. Corpus cancers with these histologic types tend to have a worse prognosis compared to adenocarcinomas. About 70 percent of all corpus cancers among US whites are adenocarcinomas compared to 53 percent among nonwhites.

Various factors have been suggested as being related to endometrial cancer risk. Among them are obesity, nulliparity, late menopause/early menarchy, Stein-Leventhal Syndrome, radiation, exogenous estrogens, and previous breast or ovarian cancers. MacDonald and Sitteri have proposed a hormonal model for endometrial cancer induction that lends biological plausibility that the association observed for a number of these risk factors may indeed be causal. The estrogens, estradiol and estrone, compete for endometrial receptor sites in vitro. Estrone has been shown to be carcinogenic both to breast and endometrial tissue, whereas estradiol may not be. Thus MacDonald and Sitteri postulate that a high estronel estradiol ratio in vivo may be causally related to endometrial cancer.

Review of the epidemiology of corpus uteri cancer can be found in the following:


MALIGNANT NEOPLASMS OF CORPUS UTERI

* = WISC. FEMALE RATE (1970-1975)
△ = U.S. FEMALE RATE (1970)
DOTTED LINES INDICATE 95% C.I. FOR WISC. RATES

ANNUAL AGE SPECIFIC MORTALITY RATE PER 100,000

AGE
CANCER OF CORPUS UTERI AND UTERUS, UNSPECIFIED

GRAPH 2

* INDICATE WISCONSIN RATE
△ INDICATE U.S. WHITE RATE

ANNUAL AGE ADJUSTED MORTALITY RATES PER 100,000

- U.S. 1950 STANDARD

MALIGNANT NEOPLASMS OF CORPUS UTERI

GRAPH 3

\[ \Delta = \text{WISC. FEMALE RATE} \]

\text{DOTTED LINES INDICATE 95\% C.I. FOR WISC. RATES}

ANNUAL AGE ADJUSTED MORTALITY RATE PER 100,000


Directly Standardized to US 1970 Population
MALIGNANT NEOPLASMS OF CORPUS UTERI

GRAPH 4

ANNUAL AGE ADJUSTED MORTALITY RATE PER 100,000

△ = WISC. FEMALE RATE (1970-1975)
BARS INDICATE 95% C.I. FOR WISC. RATES

Directly Standardized to US
1970 Population

HSA-1 HSA-2 HSA-3 HSA-4 HSA-5 HSA-6 HSA-7
I. RESULTS

A. Age specific bladder cancer mortality rates show slightly lower rates for Wisconsin females between the ages of 45 and 60 when compared to US 1970 rates. However these differences are based on only a few deaths. In general, the Wisconsin age specific bladder cancer mortality rates do not differ a great deal from the national rates. (Graphs 1 and 2)

B. Female age adjusted white US bladder cancer mortality rates show a consistent decline from 1940 to 1975. The corresponding male rates have remained fairly constant over this time period. The 1970 to 1975 annual Wisconsin female bladder cancer mortality rates are of the same magnitude as the national rates and show a general decline. This decline however is not statistically significant. The annual male bladder cancer mortality rates for Wisconsin are again similar in magnitude to the national rates. There also appears to be no clear secular trend for male bladder cancer mortality in Wisconsin. (Graphs 3, 4 and 5)

C. Comparisons between US and Wisconsin's age specific bladder cancer mortality sex ratios show a significant increase in the Wisconsin ratios between the ages of 50 and 60. This is a consequence of the slightly lower age specific rates for Wisconsin females which are based on few cases. There is little difference between the US and Wisconsin age specific sex ratio when these ratios are based on more than a few deaths. (Graph 6)

D. There no large differences in the sex specific, age adjusted bladder cancer mortality rates among the seven Wisconsin Health System Agency areas. HSA areas with relatively high male bladder cancer mortality do not have high female bladder cancer mortality as is seen for stomach and rectal cancer mortality. The lack of a pattern between male and female rates is consistent with the hypothesis of an occupationally related factor being involved with bladder cancer carcinogenesis.

E. For each sex, Wisconsin bladder cancer mortality data was fit to the multiplicative model proposed by Breslow and Day to obtain estimates for revised county SMR estimates.

1. Tests for goodness-of-fit of the data to these models indicate no apparent lack of fit, males $p = .39$, females $p = .87$. 
2. Tests to identify an overall difference between all Wisconsin county SMR values indicate no significant county differences for male bladder cancer SMR values, p = .22. However, for females the overall difference between county SMR estimates was found to be significant, p = .005.

3. Maps of Wisconsin were generated for each sex indicating the bladder cancer county SMR estimates as well as those counties with SMR estimates statistically significantly different from the rest of the state.

4. Tests for geographical clustering of counties by SMR estimate were performed. For female bladder cancer mortality, the number of pairs of contiguous counties both with low SMR estimates (lower than the 50th percentile) was found to be larger than what might be expected from chance, p = .015. A similar test for clustering of counties with high (greater than the 50th percentile) SMR estimates for female bladder cancer show no significant clustering, p = 0.80.

   Similar tests were performed for male bladder cancer mortality. Both the test for clustering of counties with high SMR estimates and low SMR estimates were not significant, p = .58 and p = .11, respectively.

   For female bladder cancer, significant clustering of counties with low SMR estimates is seen in the northcentral part of the state. The reason for such a pattern is not clear. For male bladder cancer there are higher SMR estimates in the urbanized south and southeastern part of the state. This pattern is not seen in the female bladder cancer SMR estimates. The general pattern of bladder cancer mortality in the southern part of the state is also seen in the 1950 to 1969 mortality data analyzed by Mason et al. The 1950 to 1969 female bladder cancer mortality pattern in Wisconsin is not particularly similar to that seen from the more recent data.

II. DISCUSSION

Bladder cancer accounts for approximately four percent of all newly diagnosed cancers in the United States. Within the US there is significant variation in bladder cancer mortality between counties. Generally, highly industrialized geographic areas tend to have higher rates. Apparently a sizable proportion of bladder cancer in the US is a result of environmental factors. Consequently, the identification and control of such factors may eventually reduce the frequency of this disease.

For the past 40 years United States bladder cancer mortality rates have remained nearly stable for white males and nonwhite females. There appears to be a steady increase in these rates for nonwhite males and a steady decrease
for white females. The increase seen in the nonwhite males is approaching the higher mortality rate seen for white males.

Bladder cancer morbidity data from the Second and Third National Cancer Surveys as well as from the Connecticut tumor registry show a dramatic rise in incidence for white as well as nonwhite males. For females the trend in bladder cancer morbidity is not as clear cut. The Connecticut tumor registry shows an increase in female bladder cancer while the National Cancer Survey data does not.

International comparisons of bladder cancer mortality show male rates consistently higher than female rates. Also, countries that are generally considered industrialized tend to have higher mortality rates. Within the US, the northeast (especially New Jersey) have high male bladder cancer mortality. The explanation for these high rates is not clear. The increase seen in US female bladder cancer mortality is not as great.

Increased bladder cancer risk has been associated with urbanization. Several studies have suggested that urban men have about twice the bladder cancer risk as rural men. Blot and Fraumeni's correlation study observed increased rates of bladder cancer associated with increased urbanization for both sexes in all regions of the US except for the northeast.

Several other demographic factors have been suggested as having a relationship to the etiology of bladder cancer. Among them are ancestry and socioeconomic status. At the present time there is little evidence to support a strong relationship with either of these factors.

Persons who smoke tobacco have been shown to have between two and three times the bladder cancer risk compared to nonsmokers. A dose-response relationship has been observed with duration of cigarette smoking and bladder cancer risk. Furthermore a dose-response relationship has also been seen between the number of cigarettes smoked and increased risk.

Various mechanisms have been postulated concerning how cigarette smoking could cause bladder cancer. One such indirect mechanism involves carcinogenic tryptophan metabolites. Such metabolites have been found at higher concentrations in the urine of cigarette smokers. One direct mechanism postulated involves the presence of bladder carcinogens in the cigarette smoke itself.

Increased bladder cancer risks have been demonstrated for workers in the dye industries exposed to aromatic amines, 4-aminobiphenyl, benzidine, 2-naphthylamine and 4-nitroaniline. Various other occupations have been suggested as having an increased bladder cancer risk, however, specific etiological agent(s) have not been identified. These occupations include rubberworkers, chemists, textile workers, painters, leatherworkers, printers, and hairdressers.

Other factors have been investigated regarding a link with bladder cancer. These include coffee drinking, use of artificial sweeteners, and infection by Schistosoma haematobium. Another factor that has been examined is the consumption of milk from cows who ingested bracken fern. Bracken fern is a known carcinogen. The link between bladder cancer and these factors has not yet been firmly established.
BLADDER CANCER

III. COMMENT

On the basis of the descriptive and analytic epidemiological information compiled on bladder cancer we might expect, especially among males, high SMR's for counties with large urban centers where exposure to tobacco and occupationally related bladder carcinogens is likely to be greatest. The low mortality from bladder cancer among Indians would suggest low SMR's for counties composed largely of this group.

The compiled data did not completely reflect these expectations. A significant overall difference between county SMR's was found only among the female population. For neither the male nor the female population did the geographical distribution of counties with "high" and "low" ratios reveal any pattern suggestive of etiologic clues. Menominee county, in which greater than 90 percent of the residents are Indian, was associated with the rather large county parameter estimate (SMR) of 4.65. However, this estimate is based on only two observed bladder cancer deaths occurring in Menominee county during the 1970 to 1975 period and may be considered unstable. In fact, "extreme" estimates were generally obtained only for nonpopulated counties for which few deaths were expected. The variability of these estimates is greater than that for an estimate based upon a larger population; this may explain why excess bladder cancer mortality is not indicated on the maps as occurring in the populous and industrialized counties even though such a condition might prevail. Interestingly, county estimates for males for all six urbanized industrial southeastern Wisconsin counties including Dane, Rock, Racine, Kenosha, Waukesha, and Milwaukee, had SMR estimates ranging from 1.07 to 1.37. Each of these counties had bladder cancer mortality in excess of that observed for the rest of the state. Furthermore the Health System Agency Area encompassing Milwaukee and its surrounding area (HSA-2) had the highest age adjusted mortality rate among all HSA's. Mortality from bladder cancer does appear to be higher in urban counties compared to rural areas though this increase is slight and not statistically significant. In fact, for the sixteen counties having at least one town of greater than 25,000 inhabitants, one-half had mortality higher than the remainder of the state compared to 43 percent for the 56 counties containing no town of that size. We conclude that only a slight mortality gradient can be detected in association with increasing urbanization. While exposure to etiologic agents of bladder cancer appears greater in urban settings, the distribution of these agents are probably widespread throughout Wisconsin.

Reviews of the epidemiology of bladder cancer can be found in the following:


MALIGNANT NEOPLASMS OF THE BLADDER

$\star =$ WISC. MALE RATE (1970-1975)

$\triangle =$ U.S. MALE RATE (1970)

DOTTED LINES INDICATE 95% C.I. FOR WISC. RATES

ANNUAL AGE SPECIFIC MORTALITY RATE PER 100,000

AGE

0.01  10.  20.  30.  40.  50.  60.  70.  80.  90.
MALIGNANT NEOPLASMS OF THE BLADDER

* = WISC. FEMALE RATE (1970-1975)
△ = U.S. FEMALE RATE (1970)

DOTTED LINES INDICATE 95% C.I. FOR WISC. RATES
MALIGNANT NEOPLASMS OF THE BLADDER

△ = WISC. MALE RATE
× = WISC. FEMALE RATE
DOTTED LINES INDICATE 95% C.I. FOR WISC. RATES

DIRECTLY STANDARDIZED TO US 1970 POPULATION
MALIGNANT NEOPLASM OF BLADDER

* = WISC. MALE RATE (1970-1975)
△ = WISC. FEMALE RATE (1970-1975)
Bars indicate 95% C.I. for WISC. Rates

ANNUAL AGE ADJUSTED MORTALITY RATE PER 100,000

Directly standardized to US
1970 Population

HSA-1 HSA-2 HSA-3 HSA-4 HSA-5 HSA-6 HSA-7
APPENDIX I

Assessing Differences in Mortality Between Wisconsin Counties

The method proposed by Breslow and Day\(^3\) was used to assess differences in sex and site specific mortality rates between Wisconsin counties. Their method proposed a multiplicative model for the rates which may be considered an extension of the method of "indirect" standardization which produces the standard mortality ratio (SMR).

Denote the number of individuals at risk in the \(j^{th}\) age group and in the \(i^{th}\) county by \(N_{ij}\). Similarly denote the number of cause specific deaths by \(D_{ij}\). Assuming the populations of the counties are large and that deaths are rare, the data might be represented by a Poisson model with \(N_{ij}\) fixed and \(D_{ij}\) subject to random variation according to a Poisson distribution with expectation: \(E(D_{ij}) = \lambda_{ij}N_{ij}\).

Breslow and Day propose a model where \(\lambda_{ij} = \Theta_i \phi_j\). Here \(\Theta_i\) represent the multiplicative contribution of the \(i^{th}\) county and \(\phi_j\) represent the contribution of the \(j^{th}\) age group. This model is over-parameterized in the sense that if \(\lambda_{ij} = \Theta_i \phi_j\) then for a nonzero constant, \(\alpha\), \(\lambda_{ij} = (\alpha \Theta_i)(\frac{1}{\alpha} \phi_j)\). The parameters \(\Theta_i\) and \(\phi_j\) may be uniquely identified by imposing the constraint \(\sum_j \phi_j N_{ij} = D_{++}\).

Here \(N_{ij} = \sum_i N_{ij}\) and \(D_{++} = \sum_i \sum_j D_{ij}\). Maximum likelihood estimates (MLE's) for the \(\phi_j\)'s and \(\phi_j\)'s can be obtained from the likelihood equations using iterative methods. The MLE of the \(\phi_j\)'s at the end of the first iteration is equivalent to the age specific rates for the state taken as a whole. The MLE of the \(\Theta_i\)'s at the end of the first iteration are the standard mortality ratios that are obtained when using the "indirect" method of standardization and the whole state average.
is used as the standard. In practice the final estimates for the $\theta_i$'s and
$\theta_j$'s are close to those obtained at the end of the first iteration. For
counties which have no deaths the estimate for $\theta_i$ cannot be obtained.

The goodness-of-fit of the model can be evaluated by using the chi-square
criteria $\sum(0 - E)^2/E$. Here $0 = D_{ij}$ and $E = \hat{D}_{ij} = \hat{\theta}_i \hat{\theta}_j N_{ij}$. The degrees of
freedom for the test are $(I - 1)(J - 1)$, where $i = 1, \ldots, I$ and $j = 1, \ldots, J$.
An adjustment to the degrees of freedom must be made for counties without deaths.

A test of overall differences between counties can be made by testing
$H_0: \text{all } \theta_i = 1$. This hypothesis can be tested based on differences in the
log-likelihood function evaluated at the start of the first iteration (here all
$\theta_i$'s = 1) and the end of the last iteration. Twice this difference is asymp-
totically distributed as a chi-square with $I - 1$ degrees of freedom. Again, the
degrees of freedom will need to be adjusted if there are counties with no deaths.
The counties with $\hat{\theta}_i$ (SMR) in the top ten percent and bottom ten percent were
shaded accordingly on the Wisconsin maps included in this report.

Another test of interest is whether each particular county's rates are
different than the rates for the rest of Wisconsin. One method of assessing
this difference is to use the model $E(D_{ij}) = \theta_i \theta_j N_{ij}$ where $i = 1$ or 2. Now
$i = 1$ for describing the particular county of interest and $i = 2$ for describing
the rest of the state excluding the particular county. Then $H_0: \theta_1 = \theta_2$ is of
interest. This hypothesis can again be evaluated based on difference of the
log-likelihood functions evaluated at the first and last iteration. Twice
the difference is asymptotically chi-square distributed with 1 degree of
freedom. Counties where this hypothesis is rejected at level $\alpha = .05$ are
shaded as having rates significantly above or below the rest of the state on
the Wisconsin maps included in this report. When a county has no deaths from
the specific cause of interest this test cannot be performed. Instead, significance is assessed by calculating the probability of no deaths in the county assuming the number of deaths at each age group follows a Poisson distribution. The county was shaded significantly below the rest of the state if this probability was less than 0.025.

Confidence Intervals for Age Specific Sex Ratios

The sex ratio is defined as the ratio of a male rate to a female rate. In this case the cause mortality sex ratio for various age groups is examined. The sex ratio can be estimated by estimating both the age specific male and female mortality rates and dividing.

Let $D_m$ and $D_f$ be the observed number of deaths for men and women, respectively. Let $N_m$ and $N_f$ be the number of men and women at risk. The estimated male rate is then $D_m/N_m$, and the estimated female rate is $D_f/N_f$.

Let $p$ be the true proportion of male deaths to total deaths. Condition on the total deaths, $D_m$ is distributed as a binomial random variable with parameters $D_m + D_f$ and $p$. A 95 percent confidence interval for $p$ is then:

$$\hat{p} - 1.96\left[\hat{p}(1-\hat{p})/(D_m + D_f)\right]^{1/2} < p < \hat{p} + 1.96\left[\hat{p}(1-\hat{p})/(D_m + D_f)\right]^{1/2}$$

where $\hat{p} = D_m/(D_m + D_f)$.

The estimated sex ratio is:

$$\left(\frac{D_m}{N_m}\right)/\left(\frac{D_f}{N_f}\right) = \left(D_m/D_f\right)\left(N_f/N_m\right) = (\hat{p}/(1-\hat{p}))\left(N_f/N_m\right).$$

A confidence interval for this ratio may be obtained by substituting the upper and lower values for the confidence interval around $p$. 
APPENDIX II

A Method for Identifying Geographical Clustering of Counties

A statistical test was developed to aid in identification and verification of geographical patterns in county SMR estimates. For each site and sex the counties were divided into two equal groups on the basis of their individual SMR estimates. Regardless of each county's population size, under the hypothesis of no geographical differences in risk, there is an equal chance for each county to be in either group. The number of pairs of contiguous counties both with high (or low) SMR estimates was used to assess geographical clustering. If there exists a large high risk area in the state, we might expect the number of pairs of contiguous counties both with high SMR's to be large. On the other hand, if there exists a large area in the state with a low mortality risk, then the number of pairs of contiguous counties both with low SMR's might be expected to be large.

The distribution of the number of such pairs under the hypothesis of no geographical differences in risk was evaluated using computer simulation. For 10,000 trials, the Wisconsin counties were equally divided into two groups by means of a computer random number generator. In each trial the number of pairs of counties both in a specific group was counted and stored. The resulting empirical distribution was then used to determine if the actual pattern of SMR estimates for each site and sex resulted in too many pairs of contiguous counties with high or low estimates than what might be expected from chance.
REFERENCES


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