Linking Cancer and Dementia: The Importance of considering the Competing Risk of Mortaltiy

Heidi A. Hanson, Ken R. Smith, Kevin Horn, Kelli Rasmussen, Site Li, John Hoffman
University of Utah

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Introduction

Several studies have examined the association between cancer and dementia and their findings have been summarized in Figure 1. These studies are limited by failure to account for the competing risk of mortality[1-4], relatively short follow-up periods,[1-4] small sample sizes, and [3-5] reliance primarily upon prescription data for dementia diagnoses.[2] This body of work also excludes the most widely-studied primary cancer with respect to cognitive function, breast cancer.

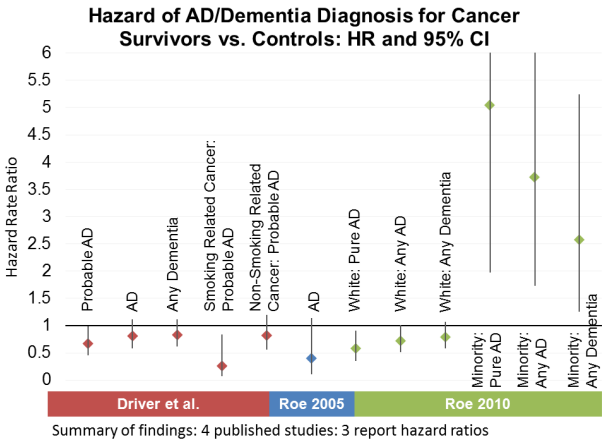


Figure 1. Summary of Published Findings[7-9]

Careful and statistically powerful studies are needed to help develop and establish public health guidelines. The availability of high quality data, appropriate measures, large samples, and interdisciplinary insights are essential elements for addressing the question. **The novel feature of this project is the unique and unparalleled data provided by the Utah Population Database (UPDB).** The UPDB is one of the world's richest sources of genealogical and medical information that supports research among many disciplines including gerontology, neurology, genetics, oncology, epidemiology, and demography. The breadth and depth of data contained within the UPDB and databases to which it is linked set it apart from the few population databases in existence,[6-8] providing a unique platform for innovative population-based analyses.[9]

Examining the inconsistencies regarding the association between cancer and subsequent dementia and AD risk can be accomplished by using UPDB for six critical reasons: (1) its coverage of an entire defined population, (2) the ability to look at early onset (diagnosis age < 65) dementia, (3) the availability of data over longer periods of follow-up, (4) its inclusion of both genders, (5) the ability to use sibling models to control for unobserved heterogeneity, and (6) the availability of familial risk measures of cancer. Unlike previous studies, our project will be based on the incidence of cancer and dementia over multiple decades allowing for greater statistical power. Our unique capability of linking Utah Cancer Registry (UCR) cancer incidence, treatment, and follow-up data to the development of AD and dementia diagnosis may prove of utmost importance in improving our understanding of this public health crisis.

Data

The data for this preliminary study come from the UPDB, Utah Cancer Registry (UCR), and linked Medicare (CMS) data. The UCR (268,536 Records, 1966-2008) is a population-based registry that has collected cancer data in the state of Utah since 1966. The UCR is an original member of the SEER program. Incident cases of cancer are identified among Utah residents based on systematic and routine review of medical records, pathology reports, radiation therapy records, hospital discharge lists, and vital records. UPDB staff have considerable experience in patient record matching.[10,11] Medicare claims data (534,542 individuals, 1992-2009) have been linked to the UPDB; therefore individuals with a UCR record have also been linked to their Medicare records.

The sample selected for this set of preliminary analyses includes 144,847 individuals (66,057 males; 78,817 females) age 65+ and enrolled in Medicare Parts A/B for the full 18 year period of observation or death. All individuals in this sample were required to be Medicare

eligible in 1992, have no dementia diagnoses in 1992 or 1993[1], and link to the UPDB. An incident case of dementia was defined as the first observation of a dementia claim[2] after the 2 year 'black-out' period.

The results reported in this report are descriptive. We plan to account for the competing risk of death, family history of cancer, and other demographic variables when studying the relationship between cancer and dementia in later versions of this paper. Standard survival analysis techniques rely on the assumption that competing risks of censoring (death) are independent of each other.

In future analyses we plan to use competing risks[12] models to adjust the hazard ratios for the competing risk of mortality and rely on a standard modification to the Cox model analytic approach applied to dementia onset. Familial patterns of susceptibility to cancer provide clues to the relationship between the genetic and environmental components of the link between cancer and dementia. The relationship between cancer and dementia may be stronger for those without a family history of cancer because it suggests a strong environmental component to the cancer. There may be a null or negative association between cancer and dementia for those with a high familial risk of cancer, due to pleiotropic mechanisms as suggested by Driver[5] or that the genetic mutation that predisposes individuals for cancer does not affect dementia risk. The genealogical data linked to UCR and death certificate data in the UPDB can be used to assess familial risk of cancer.

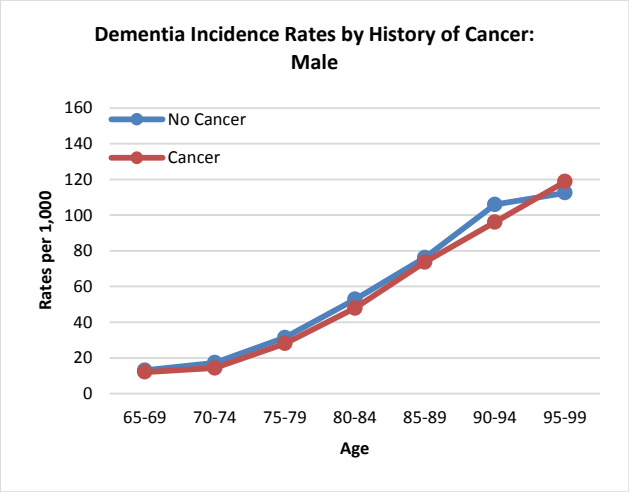
Results

Figure 2 shows dementia incidence rates by age for males and females, respectively. In conjunction with previously reported studies, we find little difference in dementia incidence for individuals diagnosed with cancer and those without a history of cancer for both males and females. For males, we see that dementia incidence rates are slightly smaller for individuals with cancer compared to those without for males between the ages of 80 and 94. The difference in incidence rates by cancer history for females, with the exception age 95 – 99, is also quite small.

While understanding the overall association between cancer and dementia is important, it is imperative to test this relationship for multiple types of cancer. Understanding the association between cancer and dementia across multiple sites will contribute information about the possible biological mechanisms linking cancer and dementia. In addition, as we will show below, comparing dementia rates across cancers with differing mortality rates also allows lends some information to the importance of considering mortality selection.

[1] A two year 'black out' period was used to identify incident cases. Individuals with dementia would have likely had a record with a dementia related claim during this two year period. We assume that any individual without a dementia diagnosis during this period had not ever been diagnosis with aging related dementia.

[2] ICD9 codes 290.xx, 294.1, 331, 331.x, 331.2, 331.89, 331.9, 331.0, and 797. We plan to refine this measure (ever/never) in later versions of the analysis. For example, requiring an individual to have multiple claims in a 6 month period.



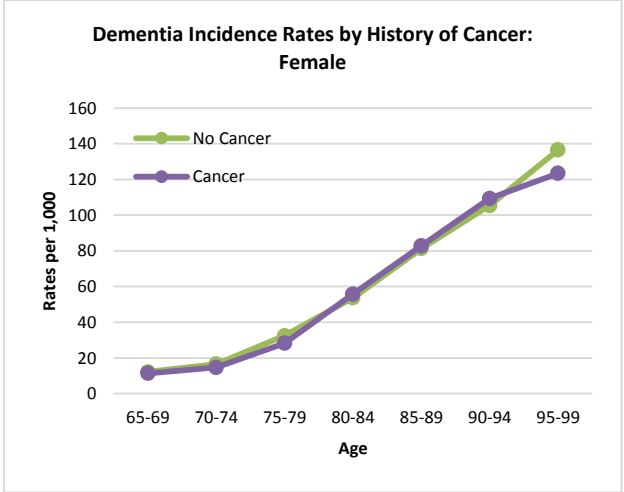


Figure 2

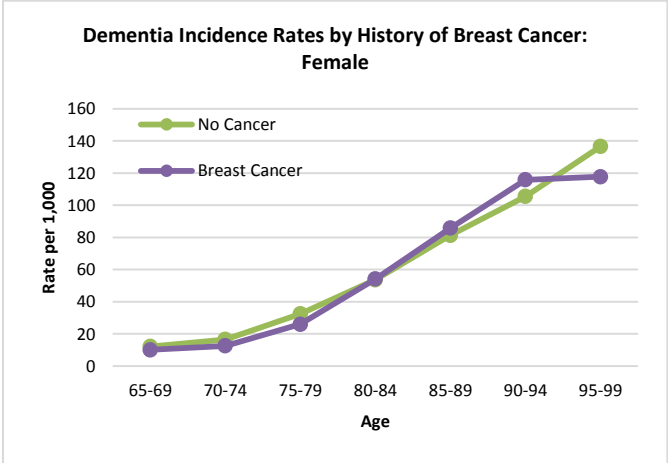


Figure 3

Figure 3 shows the incidence of dementia by history of breast cancer (five year survival rate of is 89.2%[3]). We show that women with a history of breast cancer have lower rates of dementia early on, but that this relationship inverts after age 80. Overall, there appears to be little difference in the rates of dementia between women with a diagnosis of breast cancer and those never diagnosed with cancer. However, more research should be done to further investigate these patterns.

[3] All survival statistics were pulled from the SEER website: http://seer.cancer.gov/statfacts/html/prost.html

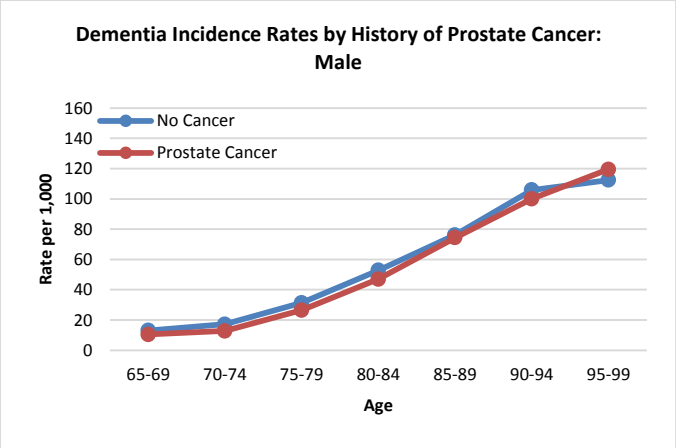


Figure 5

Figure 5 shows the incidence of dementia by history of prostate cancer (five year survival rate of 99.2%). Again, we see that there are very small differences in dementia between men with a diagnosis of prostate cancer and those never being diagnoses with cancer.

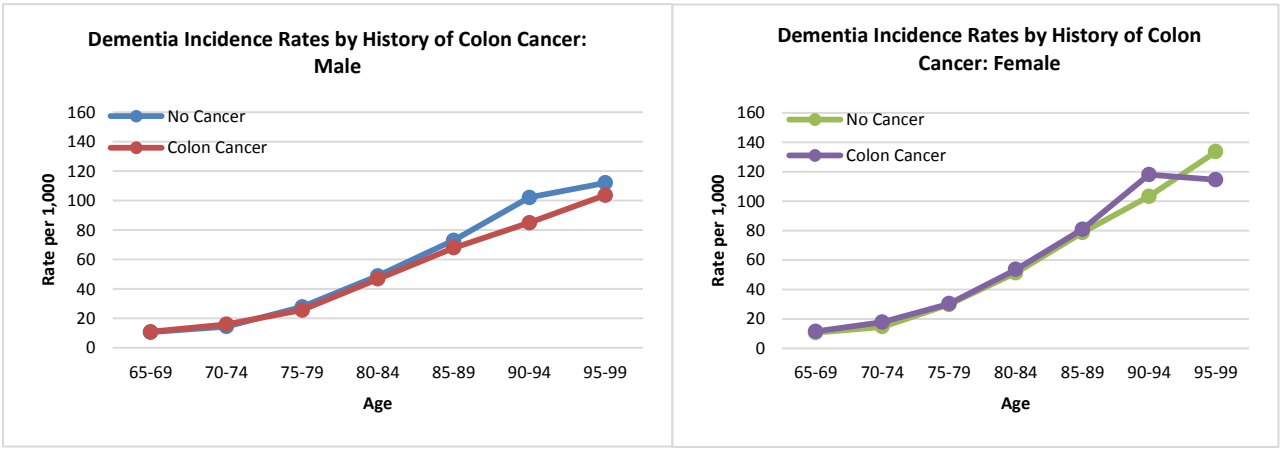
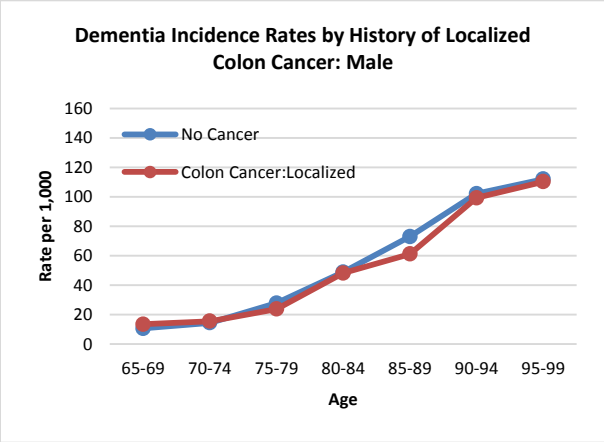


Figure 6

Figure 6 shows the dementia incidence rates by history of colon cancer. We find small differences in dementia rates for men with and without colon cancer at older ages, but overall there rates are very similar. Cancer stage at diagnosis is a strong predictor of 5 year survival. The five year survival for localized colon cancer is approximately 20% higher for localized vs. regional cancer (90.3% vs. 70.4%). If mortality selection is biasing the results, we would expect to see a difference in dementia incidence rates by stage at diagnosis. Figures 7 and 8 show dementia incidence rates by ever/never diagnosed with colon cancer at localized and regional stages, respectively. There is very little difference in rates of dementia for individuals diagnosed with a localized colon cancer. Individuals with a regional colon cancer diagnosis (70.4% 5-year survival rate) have lower rates of dementia compared to the population with no history of cancer. These results support the notion that mortality selection biases these results and

should be considered when studying the relationship between cancer and dementia. It also highlights the importance of considering site and stage.



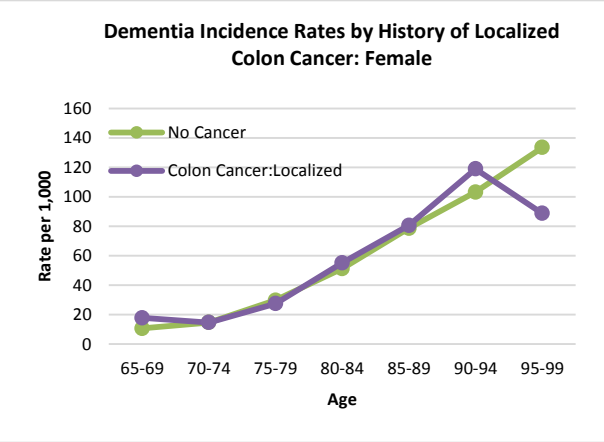
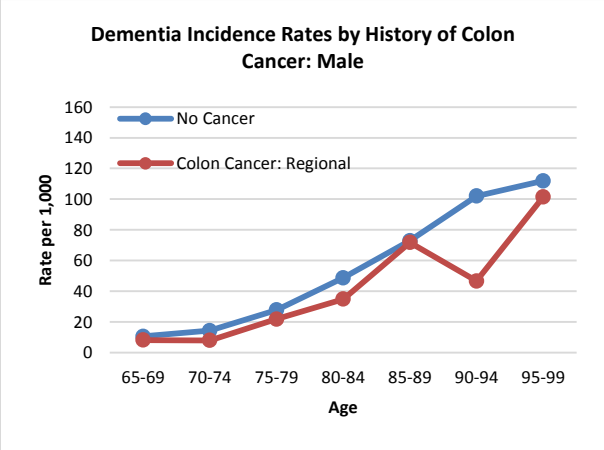


Figure 7



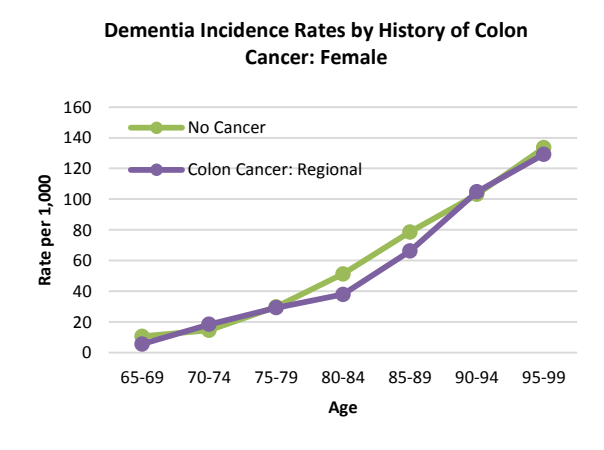


Figure 8

Figure 9 shows the dementia incidents rates by history of lung cancer for males and females, respectively. The 5-year survival rate for lung cancer is approximately 17%. For males, the high mortality associated with lung cancer may explain the large difference in dementia incidence between individuals ever diagnosed with lung cancer and those never diagnosed with lung cancer and future studies researching the relationship between cancer and dementia should correct for this bias. The pattern for females is quite different, with a gradual rate of increase in dementia with age for women ever diagnosed with lung cancer. Women with a history of lung cancer have higher rates of dementia in the younger age categories and lower rates of dementia in the older age categories. Some of the differences between males and females can likely be explained by cohort differences in smoking. Smoking prevalence for females in the birth cohorts represented in this study (1892 – 1927) was quite low, while

smoking prevalence rates by birth cohort are at their peak levels for men represented in this study (http://cancercontrol.cancer.gov/brp/tcrb/monographs/8/m8_2.pdf).

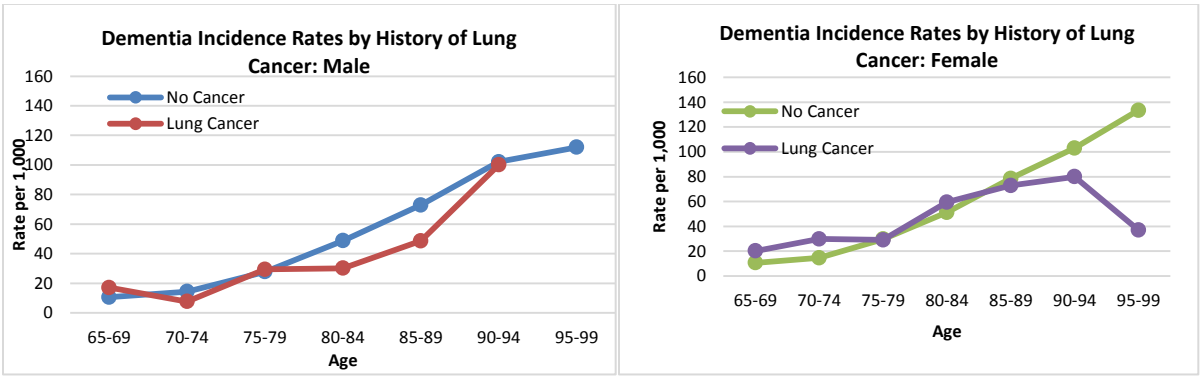


Figure 9

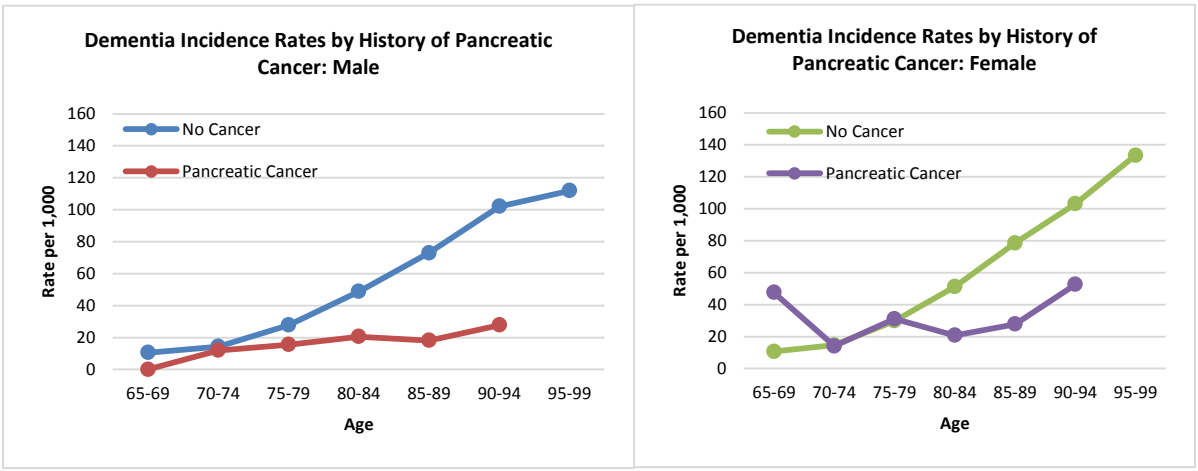


Figure 10

Figure 10 shows the incidence rates of dementia by history of pancreatic cancer for males and females, respectively. Pancreatic cancer is much less prevalent than the other cancers presented here, with an incidence rate of 12.2 cases per 100,000 in the population per year. However, it is particularly interesting because the 5-year survival rates are minuscule (6%). Individuals diagnosed with pancreatic cancer likely do not live long enough for a subsequent incidence case of dementia to occur. And as expected, this figure shows much lower rates of dementia for individuals ever diagnosed with pancreatic cancer.

Conclusions

The data presented here suggest that studies not formally accounting for mortality selection may lead to biased results. We show that there are negligible differences in dementia incidence by age for cancers with high survival rates. As the lethality of the cancer increases, the seemingly 'protective' relationship between cancer and dementia increases, however

individuals with these forms of cancer likely do not live long enough to have a subsequent diagnosis of dementia.

Any analyses of an association between two morbid medical conditions in an elderly population must introduce aggressive controls to assess the effects of competing risks. In the case of cancer incidence altering the risk of dementia, it is plausible that dementia risks are low for those diagnosed with cancer because their mortality rates are higher than unaffected controls and hence have less opportunity to develop dementia. This proposal will examine this problem specifically through the use of competing risks with dependent and independent hazards and cumulative incidence curves.

The threats to validity originating from the unadjusted adverse effects of competing risks are rivaled by the problems raised by uncontrolled confounding factors. While no observational study can account for all sources of confounding variables, a unique advantage of the UPDB is its ability to leverage family-level data (e.g., sets of siblings) as a means for statistically controlling for unobserved familial factors that may account for the association between cancer and dementia risk.

This population-based study will advance our knowledge about the association between dementia and cancer based upon the strengths of its analysis, its use of high quality regional data from very large representative sample size spanning decades, its use of data on siblings, and its measures of familial risk of cancer

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