Aging and Cancer Mortality: Dynamics of Change and Sex Differences

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Abstract

Age-related changes in cancer mortality risk are important for understanding the processes of disease and aging interaction. The extent to which these age changes differ by sex further contributes to this understanding but has not been well studied to date. We conducted a systematic examination of dynamics and heterogeneity of age changes in cancer mortality rates for the top 14 cancer sites using vital statistics from the NCHS and SEER between 1969 and 2007. We assessed patterns of age changes in site-specific mortality rates in terms of both increase (age slope) and acceleration (change in age slope) as measured by the log-log acceleration rate (LLA). We assessed sex differences in mortality rates through sex mortality rate ratios and sex differences in age changes through comparisons of the LLA by sex. The logged male-to-female mortality ratios are positive but vary substantially with age in magnitude. And the age patterns of sex ratios also vary across sites. The LLA values show similar declines and hence slowdowns of mortality increment into or during old age for both sexes for most sites and periods. Post-reproductive changes in sex differences in cancer mortality are not entirely consistent with the estrogenic hypothesis about the anticarcinogenic effects of sex hormones and suggest the utility of the multistage model of disease progression for some tumor sites. Analysis of age dynamics and sex differences in cancer mortality may modify extant aging-related theories of carcinogenesis and frame future searches for specific explanatory factors.

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1. Introduction

As the second leading cause of death in the United States and the disease most prevalent in older people, cancer is killing an ever increasing number of Americans as the population ages. The relationship between cancer and aging, in this context, becomes increasingly important for the understanding of not only cancer etiology but also the prospect of human longevity. The fact that cancer incidence rates increase dramatically in late life in mammalian species suggests potential common causative mechanisms shared by cancer and aging such as genetic instability leading to improper gene regulation (Cutler and Semsei 1989). There is also considerable evidence that cancer incidents slow at advanced age which are similar to the old-age deceleration of all-cause mortality and further suggest that the processes of cancer and senescence might be closely related (Frank 2007; Manton and others 2009). To more fully understand this relationship in humans, however, we need more direct assessment of the age dynamics of cancer mortality that link rate of cancer death with rate of aging at the population level. In addition, population heterogeneity and cancer site provide clues to physiological and behavioral processes leading to mortality but have not been systematically examined in relation to aging. This study focuses on sex differences and mortality from leading cancer sites that can further inform the specific mechanisms underlying the process of disease and aging interaction.

Sex differentials in mortality, namely female advantages in survival, have been widely observed across time, space, cause of death, and even species (Austad 2006; Carey and Liedo 1995). This pattern applies to cancer related mortality. It has been shown that males are at much higher risks of cancer incidence and mortality for a vast majority of sites (Cook and others 2009; Manton and others 2009) that largely result from cancer etiology instead of prognosis (Cook and others 2011). The higher male incidence rates, from the point of view of evolutionary biology of
aging, may reflect sex differences in strategies of “fighting external stress” in males and “fighting physiological aging” in females (Arbeev and others 2005). In addition, the prominent male excess in cancer mortality risk has been expected to result from sex differences in physiological risk factors such as gonadal hormones. Specifically, estrogen may protect women at the cellular level in terms of immune competence, fat and glucose metabolism, and carcinogenic susceptibility (Cook and others 2011; Yang and Kozloski 2011). While a number of physiological and behavioral factors have been proposed as potential explanations for this pattern, a full understanding of the origins and mechanisms in sex differences in cancer as well as all-cause mortality has remained elusive (IOM 2001). We argue that studying how sex differences in cancer mortality risk unfold with aging provides one important avenue toward an improved account of why women live longer than men.

Whereas prior research on this topic focused on the differences in mortality risk within age groups instead of across age groups, there appear to be age-associated changes in sex mortality differentials that remain poorly documented and understood. For instance, studies of both historical data from vital statistics and recent nationally representative survey data show that the positive male-to-female mortality rate ratios in young adulthood decreased in older age for all causes of death except cancer, in which case the ratios increased indicating greater male excesses in cancer-related deaths in late life (Austad 2006; Yang and Kozloski 2012). Given the physiological pathways to intrinsic mortality shared by degenerative diseases, this difference seems an anomaly that requires further investigations. Taking age changes into account may modify extant understanding of carcinogenesis and cancer progression in different sites of origin. For instance, the same “estrogenic hypothesis” that is used to explain the female advantage in cancer survival also implies female increases in cancer mortality risk after middle ages due to the
loss of those physiological advantages after the reduction of estrogen. That is, sex differences in age pattern of fecundity decline should lead to reductions of sex cancer mortality gaps. Persistent or increasing sex gaps in cancer mortality in post-reproductive life span would be inconsistent with the hypothesis on the anticarcinogenic effects of estrogen.

While the sex disparities mentioned above are based on the metrics of mortality rate at a given age and *increase* in the rate with age (age slope), a closely related but distinct question that has been less examined is whether sex differentials also reside in cancer mortality *acceleration* with age (change in age slope). Data on cancer incidence and mortality, for example, show patterns of age acceleration that are different from age increase. While incidence and mortality risks increase with age, the increases occur more slowly or decelerate after the age of 60 (Frank 2007; Horiuchi 1997). This raises the possibility that the potential effect of menopause on cancer mortality risk is not simply reflected by age increases, which are continuous and independent of fecundity declines, but reflected by age acceleration of the mortality increase (Horiuchi 1997). The absence of sex difference in mortality acceleration would then suggest alternative mechanisms that apply to both sexes such as the multistage cancer progression and aging model. Therefore, age variations contribute to the complexity of explanations of sex differences in cancer mortality and need to be systematically examined in population-based studies. Such examinations are particularly useful for testing extant hypotheses or generating new ones on the causes of sex disparities in mortality in relation to cancer etiology and exposures and vulnerabilities to carcinogens related to constitutional endowment, reproductive biology, and social behaviors.

In sum, there is a lack of studies that compare sex differences in both mortality increase and acceleration. And empirical findings from a few prior studies are suggestive of old age
changes in the sex gap in cancer mortality but are limited in the coverage of historical period, cancer sites, or number of cancer related deaths (Cook and others 2011; Horiuchi 1997; Yang and Kozloski 2012). This study fills these gaps through systematic examinations of dynamics and heterogeneity of age changes in cancer mortality using vital statistics that span four decades. We assess both age increase and age acceleration in cancer mortality rates and sex differences in these age dynamics for the top 14 cancer sites with diverse etiologies and age trajectories of progression to mortality.

2. Material and Methods

2.1 Data

We obtained the U.S. cancer mortality data collected by the National Center for Health Statistics (NCHS) using the NCI’s Surveillance, Epidemiology, and End Results (SEER)*Stat software for the period 1969 to 2007 (Surveillance Epidemiology and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Mortality - All COD). We examined all cancer sites combined, all cancer sites excluding sex-specific and breast, and 14 leading causes of cancer deaths (Jemal and others 2008), including cancers of the lung and bronchus, colon and rectum, pancreas, esophagus, urinary bladder, liver and intrahepatic bile duct, kidney and renal pelvis, stomach, brain and other nervous system, oral cavity and pharynx and melanoma of the skin, leukemia, non-Hodgkin lymphoma, and myeloma. The International Classification of Disease (ICD) versions changed over this time period (ICD-8 to ICD-10). The underlying causes of death are based on the death certificate information reported to the CDC National Vital Statistics and categorized according to SEER site groups to ensure comparability among ICD versions (Jemal and others 2008). The SEER cause of death recode is listed at
Denominators in the death rate computation are from county-level population estimates that were summed to the state and national level. More detailed description of the methodologies used for the population estimates by the Census Bureau and the NCI is available elsewhere (Jemal and others 2008).

2.2 Death Rates and Sex Mortality Ratio

For each period spanning a decade or part (1969-1979, 1980-1989, 1990-1999, 2000-2007), we constructed age-specific death rates by site for each sex as the number of deaths per 100,000 person years at exposure between the ages of \( x \) and \( x + 5 \), which we denote as \( 5M_x \). We present results for ages 30 to 85+ due to much smaller numbers of deaths in younger ages and correspondingly low and unstable death rates. To compare sex differences in mortality increase, we calculated the logged male to female ratios of death rates at each age. Use of logarithms provides a scale-free measure of difference. Because the size of the sex ratio will depend on the choice of numerator, taking the log of the ratio makes it symmetrical. Positive values of the logged ratio indicate higher male mortality rates relative to female mortality rates; negative values indicate lower male relative to female rates.

2.3 Measure of Aging Rate: Log-log Acceleration Rate

We further compare sex differences in mortality acceleration as measured by the log-log acceleration rate (LLA). The LLA is defined as the percentage change in mortality rate relative to percentage change in age (Frank 2004a; Frank 2004b):

\[
LLA(x) = \frac{d \mu(x)/\mu(x)}{dx/x} = \frac{d \log \mu(x)}{d \log x}
\]

where \( \mu(x) \) is the force of mortality at exact age \( x \). The LLA relates to the life table aging rate (LAR) commonly adopted in studies of overall mortality (Carey and Liedo 1995) as a measure of relative mortality increase. While the LAR is a scale-free rate relative to scale-specific age, the
LLA is scale-free in both rate and age. Additional analyses show highly consistent results using the LAR and LLA. We only present those based on the LLA in the interest of space. The value of the LLA at a given age indicates the rate of mortality increase with respect to age. A higher LLA for the male population than for the female population thus indicates faster male than female relative mortality increase. The slope of the LLA indicates rate of change in mortality increment. That is, an increase in the LLA indicates acceleration in relative mortality increase, whereas a decline in the LLA indicates deceleration in the increase. Similar to the LAR, the LLA can be estimated with data on age-specific death rate by (Horiuchi 1997; Horiuchi and Coale 1990):

\[
\hat{LLA}(x) = \left[ \log \frac{M_x}{M_{x-5}} - \log \frac{M_{x-5}}{M_{x-10}} \right] / \left[ \log(x) - \log(x-5) \right]
\]

The LLA can also be related to the multistage model of carcinogenesis and lends itself to the depiction of cancer progression and the related aging and mortality processes. Genetic and morphological studies of cancer suggest that a tumor progresses through a sequence of stages. The multistage theory of carcinogenesis, initially developed in the 1950s (Fisher and Hollomon 1951; Nordling 1953), has been used to mathematically describe the progression of cancer (Frank 2007; Manton and others 2009). Assuming that the development of cancer requires \( n \) independent stages at the probability \( p \) of experiencing each, it has been shown that the age-specific cancer incidence or mortality rates can be fit to a Weibull model: \( \mu(x) = \frac{p^n x^{n-1}}{(n-1)!} = \alpha x^{n-1} \). Taking log transformation to both sides of the Weibull function, one can derive that the LLA is equal to the slope \( n-1 \). Therefore, the deceleration in cancer incidence or mortality rate with age indicated by the decline in the LLA has been proposed to result from surviving population concentrating in the fewer and fewer remaining stages (Frank 2004a).
3. Results

3.1 Age-specific Cancer Mortality Rates

Age-specific mortality rates for all cancer sites combined and by site for periods of 1969-79 and 2000-07 are shown in Figure 1. Those for the middle two periods are largely similar in shape and omitted in the interest of space. For both sexes, the age-specific mortality rates generally increase steadily from the age of 30 to the 70s. Old-age decreases in mortality rates across both periods are evident for some sites such as lung cancer, brain cancer, and myeloma. Patterns of age acceleration or deceleration can be discerned but will be better described by the analysis of the LLA. Figure 1 indicates prominent male excesses in cancer mortality rates. Correspondingly, the logged sex (male-to-female) mortality ratios shown in Figure 2 are positive for all ages and sites.

3.2 Sex Differences in Cancer Mortality Rates

Figure 2 also suggests that there are substantial age variations in the sex differences in mortality rates for all sites and historical periods. Consistent with previous research of total cancer mortality (Yang and Kozloski 2012), the male excess increased continuously from younger adulthood into old ages. For all cancer sites excluding sex-specific and breast, an old age decrease or leveling of the sex gap becomes more apparent. This suggests that the old age increases in male excesses for all cancer sites combined are partly due to differences in cancers of reproductive tissues, especially prostate cancer mortality that increased markedly in old age for men and female breast cancer mortality that increased more before old ages than the other cancers. While the male excess increases almost linearly with age for lung cancer mortality and relatively continuously with age in the two most recent periods for skin cancer mortality, the age...
patterns of the sex ratios follow three types of trajectories for other sites. A pattern of increases followed by decreases in old age is evident for cancers of colon and rectum, urinary bladder, liver, kidney, stomach, oral cavity, and leukemia, with varying peak ages. The opposite pattern of change marked by decreases followed by increases in old age is found for brain cancer and myeloma. Continuous decreases are found for cancers of esophagus, pancreas, and non-Hodgkin lymphoma.

[Figure 2 about here]

The considerable regularities in the shapes of age patterns of sex ratios across periods suggest both a developmental and a biological basis for the sex differences in cancer mortality. Relatively large changes in the magnitude of sex gaps over time have occurred for a few cases that suggest additional period-specific influences on exposures to carcinogens and detrimental lifestyle factors. The male-to-female rate ratios for all cancer deaths combined decreased across time, largely because of the period pattern in mortality from lung, pancreatic and stomach cancers due to female increases in cigarette smoking in more recent decades (Yang 2008). Period increases in male excesses are evident for colorectal, esophageal, liver, and skin cancer mortality, which suggest disproportionate male increases in relevant risk factors such as high fat diet, alcohol consumption, Hepatitis B virus and/or Herpes simplex virus infections, and UV exposures (Manton and others 2009). For the remaining sites, the sex ratios remained relatively constant or fluctuated slightly with time. Evidence so far is not entirely consistent with the estrogenic hypothesis in that only 3 out of the 14 cancer sites (colorectal, stomach cancers, and leukemia) show post-reproductive decreases in male excesses in mortality across all periods, whereas age changes in the sex mortality ratios for the other sites are either in the opposite
direction or show initiations of declines before middle ages that cannot be attributed to the hypothesized effects of estrogen.

**3.3 Mortality Acceleration: Age Patterns of LLA and Sex Differences**

The sex mortality ratios based on mortality rates concern mortality levels and increase in absolute terms. We next examine male and female dynamics of mortality change in relative terms. Figure 3 presents the age patterns of mortality acceleration as measured by the LLA.

![Figure 3 about here]

**3.3.1 All Cancer Sites Combined**

As shown in Figure 3 for all cancer sites, an LLA for males at the age of 40 in the 1970s is estimated to be 5, meaning that the total cancer death rate is increasing at the rate of 5% per percentage change of age. The LLA for both sexes decreased after the age of 45, indicating that the relative cancer mortality increase decelerated. And the decline towards zero at very old age, known as the old-age mortality plateau, is also evident in all-cause mortality (Horiuchi and Wilmoth 1998). According to the multistage hypothesis of cancer progression, the rise in acceleration in early to middle life is due to increasing rates of transition between stages of the disease, whereas the late-life decline in acceleration of cancer mortality rates may result from the concentration of older individuals with few stages remaining (Frank 2004b; Frank 2007). The LLA for the 1970s show a more pronounced female slowdown in mortality deceleration after the age of 60 that was also observed in other national populations such as England, Wales and Italy during the same historical period (Horiuchi 1997), but the female slowdown largely disappeared in subsequent periods. The lower LLA for females compared to males at most ages indicate that the percentage mortality increase of all cancer sites was slower for females relative to percentage change in age. But the similar slope changes in the LLA indicate that the extent of cancer
mortality acceleration does not differ much between the two sexes. The lack of a consistent postmenopausal mortality acceleration for females across time cautions against a straightforward explanation of the correlation between estrogen and malignancies.

3.3.2 All Cancer Sites Excluding Sex-specific and Breast

The next set of results on all cancer sites, excluding sex-specific and breast, helps to further isolate the carcinogenic or anticarcinogenic effects of sex hormone profiles. The two sexes show closer values of LLA and hence mortality increase in two recent decades, suggesting the much greater cancer mortality increase for males (as mentioned before for all sites combined) is due to prostate and possibly other male-only cancers. However, the slope changes in LLA estimates for cancer deaths common to both sexes suggest a remarkable resemblance with those for all cancer sites combined. The sex differences, or the lack thereof, in the age patterns of mortality acceleration in post-reproductive life span are therefore not likely due to the age patterns of cancers in reproductive or breast tissues.

3.3.3 Cancer by Site

Results from site-specific analysis show greater male mortality increases with age (higher male LLA) for lung, colorectal, leukemia, urinary bladder, and stomach cancers for most ages but greater female mortality increases with age (higher female LLA) for pancreatic, non-Hodgkin lymphoma, and kidney cancers. The sex differences in mortality increase are ambiguous for other sites. Most individual sites show age patterns of mortality acceleration that indicate continuous declines (deceleration of mortality increase) into or during old age for both sexes in the LLA. A greater degree of female mortality acceleration after middle age, as predicted by the estogenic hypothesis, is found in a few cases, including lung and urinary bladder cancers in the 1970s, liver cancer in the 1970-1980s, colorectal and stomach cancers
after 1970s, and esophageal cancer. It is also possible that the gradual disappearance of female disadvantage in more recent periods is related to the widespread use of hormone replacement therapy in postmenopausal women in the U.S. (Hemminki and others 1988). However, that same therapy has been found to increase the risks of female cancers (Manton and others 2009). Period differences across cancer sites suggest the need to further examine the role of hormone replacement therapy as one potential factor responsible for the post-reproductive convergence in male and female patterns of mortality acceleration.

4. Discussion

The processes underlying cancer and aging are undoubtedly more complex than what this single study is able to capture. Variation across cancer sites further contributes to this complexity as each site involves specific risk factors. Our aim, however, is to identify some regularities among all cancer sites that may bear theoretical relevance to the study of aging and chronic disease. Through a systematic analysis of the age dynamics of cancer mortality rates and sex heterogeneity therein, this study has expanded previous studies on age changes in cancer incidence to shed new light on the relationship between aging and cancer mortality. While the shapes of the age changes in mortality risks vary by tumor site, the mortality acceleration followed by the old-age deceleration is common to both sexes across all time periods for most sites, suggesting the similar aging related processes underlying cancer incidence. The mortality acceleration pattern for cancer shown here is consistent with the earlier theoretical expectation that cancer and aging share genetic instability as the common mechanism (Cutler and Semsei 1989) and also consistent with the acceleration pattern for the overall mortality that can be
attributed to deterioration of the damage repair and prevention system proposed by recent biodemographic research (Horiuchi 2003).

Further, the multistage theory of disease progression can be applied to explain the subsequent deceleration in older ages. If, as suggested by the theory, the LLA is closely related to the stage parameter $n$ and thus has underlying biological meanings, the finding that the age patterns of cancer mortality acceleration vary much more across sites than within sites imply that the pathologic process leading to mortality is quite robust, yet unique, for each cancer site. It should be noted, however, that the age patterns of cancer mortality are more varied than those of incidence fit to the multistage cancer progression model. Somewhat unexpected from the multistage point of view explaining the old age decline in incidence acceleration, mortality rates of colorectal (in 1990s and 2000s), urinary bladder (after 1970s), stomach (after 1970s for females) and oral cavity cancers show accelerations during old age, while skin cancer mortality does not suggest a clear age pattern of mortality acceleration or deceleration. It is thus possible that mortality risks associated with these three cancers are not entirely explained by their incidence patterns. Additional factors related to cancer prognosis and survival need to be considered in future research toward a more general theory of disease progression and mortality.

Two major findings emerge regarding the sex differences in cancer mortality in relation to aging that require further consideration. First, the male excess in level of cancer mortality rates, previously conceived as universal across the life course, actually varies greatly with age. The myriad of distinct age trajectories of sex gaps in cancer mortality rates by site and period discourage a simplified and static view of male disadvantages in cancer survival and frame future searches for explanatory factors that are more selective and specific. Second, although the age patterns of mortality acceleration vary considerably from one cancer site to another, they are
It follows that changes in sex differences of cancer mortality largely reside in changes in the absolute levels of male and female cancer mortality rates but not changes of their shapes for most sites. These results on sex differences and their age variations provide interesting puzzles for future investigations to solve.

First, an increasing male excess in level of mortality rates (measured by sex mortality ratio) in some sites and the lack of sex differences in old age cancer mortality acceleration (measured by the LLA) are not entirely consistent with the estrogenic hypothesis that predicts a postmenopausal acceleration of female mortality increase and reductions of sex differences. At the population level, the small numbers of cancer sites and time periods in which the post-reproductive reductions of sex mortality gaps occurred do not strongly support the anticarcinogenic role of estrogen as hypothesized in prior research (see, e.g., a review by Cook and others 2011). Instead, the findings here suggest that the influences of hormone profiles on non-reproductive cancer mortality are relatively weak and much less widely applicable across sites than conventionally assumed. The post-reproductive reductions of sex differentials in mortality found in previous studies are, however, consistent for causes such as cardiovascular, infectious, and other chronic diseases which are more closely related to circulatory and immune functions regulated by sex hormone profiles (Horiuchi 1997; Yang and Kozloski 2012). It is possible that cancer is a unique body of diseases which bear more complex relationships to reproductive apparatus. It also implies that cancer maybe more tightly intertwined with the aging process itself than other diseases as both cancer and aging have been conceived as resulting from impairments of gene regulation that may not be sex-specific (Cutler and Semsei 1989). In addition, future research should focus more on age-related changes in social behavioral factors such as smoking, substance use, and neighborhood conditions that may alter exposures to
environmental carcinogens as well as genetic factors, morphological indicators of tissue growth, damage, and repair that determine cancer progression.

Second, to the extent that the old age decline of cancer mortality acceleration resembles the age pattern of all-cause mortality (Horiuchi and Wilmoth 1998), the selective survival process is a candidate explanation (Vaupel and others 1979). That is, selection of the elite eliminates the frail early on, so that it decreases heterogeneity in the surviving population later in life. While this certainly can apply to cancer mortality in old ages, the results on sex differences suggest additional and more complicated explanations because the sex gaps generally increased in level of mortality rates and persisted in rate of age acceleration. Exclusion of sex-specific sites partially explained the increases in sex gaps in level of mortality rates with age but not persistent sex differences in age acceleration. The absence of convergences in sex gaps in cancer mortality does not seem to agree with the reduced population heterogeneity brought about by the selection process. The differential selection processes by sex remain a possibility for future studies.

The existence of cohort effects on cancer mortality may confound period patterns, particularly for sites influenced by behavioral risk factors such as smoking which show pronounced sex and cohort differences (Yang 2008). We compared the sex mortality ratios and LLA patterns between male and female cohorts born between 1916 and 1939 for whom the age-specific data are the most complete. The cohort sex mortality ratios are very similar to period ratios. And similar to the finding from a previous analysis of overall mortality (Horiuchi 1997), we also found that the LLA estimates for male and female cohorts are lower than the period estimates due to the declining mortality levels in more recent cohorts and that cohort patterns of sex differences in cancer mortality are consistent with the period patterns, thereby not distorting
the results presented. Additional data on complete age trajectories of cancer mortality rates across all relevant birth cohorts are desirable in future investigations for a better test of the potential cohort confounding effect.
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**Figure 1:** Age-specific mortality rate for all cancer and 14 non sex-specific leading cancer sites: 1969-1979 and 2000-2007.
Figure 1 (continued).
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