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Sex Disparities in Cancer Mortality and Survival

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Abstract

BACKGROUND—Previous research has noted higher cancer mortality rates and lower survival among males than females. However, systematic comparisons of these two metrics by sex has been limited.

METHODS—We extracted U.S. vital rates and survival data from the Surveillance, Epidemiology and End Results Database for 36 cancers by sex and age for the period 1977–2006. We compared sex-specific mortality rates and male-to-female mortality rate ratios (MRRs). We also extracted case data which included age and date of diagnosis, sex, primary cancer site, tumor stage and grade, survival time, vital status, and cause of death. Relative cancer-specific hazard ratios (HRs) for death in the 5-year period following diagnosis were estimated with Cox proportional hazards models, adjusted for covariates.

RESULTS—For the vast majority of cancers, age-adjusted mortality rates were higher among males than females with the highest male-to-female MRR for lip (5.51), larynx (5.37), hypopharynx (4.47), esophagus (4.08) and urinary bladder (3.36). Cancer-specific survival was, for most cancers, worse for males than females, but such disparities were drastically less than corresponding MRRs; e.g., lip (HR = 0.93), larynx (1.09), hypopharynx (0.98), esophagus (1.05), and urinary bladder (0.83).

CONCLUSIONS—Male-to-female MRRs differed markedly while cancer survival disparities were much less pronounced. This suggests that sex-related cancer disparities are more strongly related to etiology than prognosis.

IMPACT—Future analytical studies should attempt to understand causes of observed sex disparities in cancer.

Keywords

Sex; Male; Female; SEER program; Neoplasms; Mortality; Epidemiology

Introduction

Sex is known to be an important factor in the pathogenesis, diagnosis, and prognosis of many diseases (1). Cancer is a stark example of such—the risk of malignancy is much higher in males, relative to females, for a majority of cancers at most ages (2). Exposure factors implicated in these sex disparities include hormones (3), body mass index (kg/m^2)

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(4), viral infections (5, 6), carcinogenic susceptibility (7), and health-care access and utilization (8).

Less information on potential sex differences in cancer mortality and cancer survival is available. Prior reports suggest that certain cancers are disproportionate by sex in these metrics (9–14), but no study has explicitly and systematically tested for sex differences in cancer mortality and cancer survival. These are important questions, because disparities in cancer mortality result from the combined effects of incidence and survival; if sex differences exist in cancer mortality and are the result of sex differences in cancer incidence, and not cancer survival, then such evidence may suggest etiologic clues for future analytical studies. If cancer survival is also highly disproportionate between men and women, then reasoning becomes more complex because, in addition to etiologic factors, this metric may suggest sex differences in the natural history of disease, access to medical care, response to treatment, or some combination of these.

In a previous report, we described sex disparities in cancer incidence rates in the United States using Surveillance Epidemiology and End Results (SEER) in an attempt to bring attention to sex as an important consideration in studies of cancer (2). In this complementary manuscript, we now utilize SEER and National Center for Health Statistics (NCHS) data to assess sex differences in cancer mortality and cancer survival.

Methodology

The April 2009 submission of the Surveillance Epidemiology and End Results (SEER) Program (15) mortality database in SEER*Stat v6.6.2 was used to calculate cancer mortality counts and rates per 100,000 person-years (age-adjusted in single years to the 2000 US standard population) for each cancer, stratified by sex for the periods 1977–1986, 1987–1996, 1997–2006, and 1977–2006. The National Vital Statistics System makes this data available through NCHS via SEER*Stat. Investigated cancers were: all malignant cancers, all malignant cancers excluding sex-specific (cervix uteri, corpus uteri, uterus NOS, ovary, vagina, vulva, other female genital organs, prostate, testis, penis, other male genital organs), all malignant cancers excluding sex-specific and breast, and individual cancers according to the SEER Cause of Death Recode (16). Male-to-female mortality rate ratios (MRRs) were calculated for cancers which had at least 10 deaths in each sex by using the male age-adjusted mortality rate as the numerator and the female age-adjusted mortality rate as the denominator. Confidence intervals for the male-to-female MRRs were generated in SEER*Stat (17). Graphs of male-to-female MRRs and sex-specific mortality rates plotted by age at death (ten-year age groups) were produced for each cancer. Each data point (age group) of these plots was required to have at least 25 cases for each sex. Cancers that had the most extreme (>10%) and consistent changes in male-to-female MRR over the three decades studied and a mortality rate of at least 3 per 100,000 in one of the sexes are illustrated and discussed herein (graphs for other cancers can be accessed online as Supplementary Material).

SEER 17 (18) incidence data were extracted for survival analyses. The geographic area and calendar period covered by each of these registries is available online (19). For each cancer, we extracted the variables: patient id, sex, primary site, histologic type, tumor stage, tumor grade, age at diagnosis, year of diagnosis, month of diagnosis, survival time, vital status, and cause of death from a case-listing session. Data were restricted to individuals with a single primary diagnosis of malignant cancer diagnosed during 1973–2006. Cox proportional hazards models were used to estimate the male, relative to female, hazard of cause-specific mortality, defined here as the cause of death being the specific-cancer originally diagnosed and death being within five years of cancer diagnosis. (All-cause mortality analyses for the

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five years following cancer diagnosis were also conducted, the results of which are provided as supplementary materials.) All analyses were adjusted for age at diagnosis (ten-year age groups to 80+) and stratified (equal coefficients across strata but with baseline hazard unique to each stratum) by year of cancer diagnosis (1973–1979, 1980–1986, 1987–1993, 1994–2000, 2001–2006).

Subsequent analyses adjusted for additional variables of cancer stage and grade were restricted to cancers where such information was available for at least 60% of cases that were included in the age-adjusted model. When models adjusted for age and year of diagnosis were restricted to those with stage and/or stage and grade information, similar estimates were attained, thus the maximal number of participants were retained in each of the models conducted. Log-log plots of survival against analysis time indicated that the proportional hazards assumption was upheld for each of the cancers assessed (data not shown). Data for the cancer peritoneum, omentum and mesentery were not amenable to Cox proportional hazards models due to small numbers.

Data were analyzed using STATA version 10.1 (StataCorp LP, College Station, TX). Graphs were generated using SigmaPlot version 11.0 (Systat Software, Inc., San Jose, CA).

Results

Sex-specific, age-adjusted cancer mortality rates per 100,000 person years and male-to-female MRRs are shown in Table 1 for the periods 1977–1986, 1987–1996, 1997–2006, and 1977–2006. For the vast majority of cancers studied, age-adjusted mortality rates were higher for males than females; over the entire period, the ten cancers with the highest male-to-female MRR were lip (5.51, 95% CI: 5.05–6.03), larynx (5.37, 95% CI: 5.29–5.45), hypopharynx (4.47, 95% CI: 4.30–4.65), esophagus (4.08, 95% CI: 4.05–4.11), urinary bladder (3.36, 95% CI: 3.34–3.39), tonsil (3.28, 95% CI: 3.17–3.39), oropharynx (3.05, 95% CI: 2.95–3.16), floor of mouth (2.89, 95% CI: 2.77–3.03), tongue (2.53, 95% CI: 2.49–2.58), and nasopharynx (2.47, 95% CI: 2.40–2.55). Only three cancers had a higher mortality rate in women than men: peritoneum, omentum and mesentery (MRR=0.39, 95% CI: 0.38–0.41), gallbladder (0.56, 95% CI: 0.55–0.57), and anus, anal canal and anorectum (0.78, 95% CI: 0.75–0.81). Male-to-female MRRs have changed over time for certain cancers; for example, lung and bronchus, larynx, and pancreas cancers had relatively high male-to-female MRRs in the 1977–1986 period which consistently decreased with time over the 30-year period. In contrast, the male-to-female MRRs consistently increased for several sites between 1977 and 2006, including the esophagus, skin excluding basal and squamous, and liver and intrahepatic bile duct.

Next, we examined whether sex-specific mortality rates and male-to-female MRRs changed with age from 1977 to 2006 (Figure 1a–e; Supplementary Figures 1–35, can be accessed online). Several patterns emerged. For example, laryngeal cancer mortality (Figure 1a) has been decreasing in both sexes for the majority of ages, but this trend has been more rapid in males. In addition, female laryngeal cancer mortality has been increasing in older age groups (70+ years). Both of these factors have contributed to the decline in male-to-female MRR of laryngeal cancer over the 30-year time period of analysis among those 60+ years of age. Esophageal cancer (Figure 1b) has been trending in the opposite direction with an increasing MRR being observed, particularly between the ages of 40–69 years. This has been caused by a decrease in the female mortality rate, while the equivalent rates for males have remained fairly stable. In the oldest age groups (70+ years), esophageal cancer mortality rates have been increasing in both sexes, but at a faster rate in males, resulting in increased MRRs for these age groups. Lung and bronchus cancer (Figure 1c) has been decreasing in males but has remained fairly stable, and has even increased at older ages, in females during 1977–

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2006. This has caused the male-to-female MRR to dramatically decrease for all adult age groups. Mortality from skin cancer (Figure 1d) has also been more incident in males than females. Moreover, the MRR for these cancers has been increasing in the age groups 50+ years due to increases in male mortality yet stable female mortality. Mortality rates of liver and intrahepatic bile duct (Figure 1e) follow a similar trend, although the observed increases have been substantially greater for males, relative to females, between the ages 30–59, which has resulted in a large increase in the MRR during the observed 30-year period.

Next, we examined cancer survival. Cox proportional hazards models, adjusted for age, stage, and grade, were used to test for sex differences in survival in the five years following cancer diagnosis (Table 2). A large number of cancers had higher hazards of death for men (i.e., worse survival) than women including, but not limited to, skin excluding basal and squamous (HR=1.58, 95% CI: 1.52–1.64), endocrine system (HR=1.32, 95% CI: 1.24–1.42), floor of mouth (HR=1.32, 95% CI: 1.07–1.63), anus, anal canal and anorectum (HR=1.21, 95% CI: 1.02–1.43), lymphoma (HR=1.20, 95% CI: 1.18–1.22), and lung and bronchus (HR=1.17, 95% CI: 1.16–1.18). In contrast, two sites were notable for their decreased risk of cause-specific mortality in men relative to women: urinary bladder (HR=0.83, 95% CI: 0.81–0.86) and tongue (HR=0.89, 95% CI: 0.83–0.95). Adjustment for stage and grade, when available, had moderate effects for some cancers, e.g. the HR for tongue cancer went from 1.07 to 0.89. The excess male hazards for the cancers salivary gland and skin excluding basal and squamous were attenuated when adjusted for stage. In contrast, the HRs for the two cancers ureter and anus, anal canal and anorectum were strengthened after adjustment for both stage and grade. Other cancers, such as urinary bladder had a more complicated pattern: higher risks in woman were attenuated yet persisted after adjustment for stage and grade.

Discussion

In this study we show that cancer mortality was much higher in males relative to females for a majority of cancer types (Table 1 and Figure). Conversely, cancer survival was generally similar between the sexes; even when differences were observed, these sex disparities were relatively modest.

Disparities of cancer mortality have largely paralleled those of cancer incidence, which we have described previously (2). For example, the incidence and mortality rate ratios were largely similar, differing by more than 20% for only four cancer sites (lip: MRR=5.51, IRR=7.16; salivary gland: MRR=2.32, IRR=1.59; skin excluding basal and squamous: MRR=2.30, IRR=1.43; and ureter: MRR=1.86, IRR=2.45). Qualitatively, the patterns of sex-specific mortality rates and male-to-female MRRs by age and stratified by decade (Figure and Supplementary Figures), appeared to be nearly identical to the patterns observed in cancer incidence rates (2).

This supports the idea that sex disparities in cancer mortality arise from the sex differences in cancer incidence. Examples of risk factors that have been implicated in cancer sex disparities include tobacco smoking in lung and bronchus, oral HPV infection in tongue and oropharyngeal (20–22), cosmetic and occupational UV radiation exposure in skin excluding basal and squamous (23, 24), and anal HPV infection in anus, anal canal and anorectum (6, 25). Universal mechanisms that may be causal in observed sex differences in cancer incidence and, thus, mortality include anti-oxidative capacity (26, 27), sex chromosome complement/aneuploidy/aberrations (28, 29), gene expression (30–32), hormones (33, 34), and immunocompetence (35). These issues relating to sex disparities in cancer incidence are discussed in further detail I our previous manuscript (2).

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For cancer survival, the largest sex differences occurred for the cancers: skin excluding basal and squamous; endocrine system; floor of mouth; retroperitoneum; salivary gland; small intestine; trachea, mediastinum and other respiratory organs; anus, anal canal and anorectum; lymphoma; nose, nasal cavity and middle ear; lung and bronchus; urinary bladder; and tongue. For all but the last two of these cancers, males had a higher risk of death from cancer. It is feasible that differential environmental exposures and/or physiological processes, such as sex hormones, could explain the observed sex disparities in survival (2, 36, 37).

Alternatively, observed sex differences in survival may be artifactual. In analyses unadjusted for extent of disease, lead time bias could give the false impression of sex disparities in five-year survival rates. For cancers with the largest sex differences in survival, the sex with the poorer survival almost always presented with later stage and higher grade tumors. Additional adjustment for stage and grade substantially attenuated most observed sex differences. However, it is unlikely that categorical metrics of stage and grade fully account for variation in extent of disease, thus residual confounding remains a distinct possibility.

Over-diagnosis through screening could also disproportionately affect sex-specific cancer survival. For example, a large proportion of cancer is thought to be asymptomatic and undiagnosed (38). If asymptomatic cancers tended to be diagnosed more frequently in females, relative to males, females could appear to have better cancer survival (39, 40). In support of this hypothesis, females typically present with earlier-stage, lower-grade, less-aggressive and unifocal cancers, compared with males (39), perhaps because women more readily and more often utilize health resources available to them (37, 41–44). More research on this subject is required to accurately ascertain to what degree this may play a role in sex discrepant cancer survival.

Sex differences in co-morbidity at cancer diagnosis could also skew cancer survival in favor of one sex over the other. Some (45–49), but not all (50–52), studies have suggested that males have more co-morbid conditions at the point of cancer diagnosis than do females. As co-morbidities are independent prognostic indicators, pre-existing chronic conditions may contribute to poorer cancer survival.

Of our results for specific cancers, better survival for lung and bronchus among women is noteworthy. This concurs with previous studies which have addressed this question (40, 53), the results of which have piqued the idea that estrogen receptor β, expressed in lung cancer cells, may be causal to this observation (54, 55), though various other hypotheses have also been suggested (56).

Urinary bladder cancer was unusual in that females had lower five-year survival, compared with males, an observation also made by others (8, 14). Given that US male urinary bladder cancer rates are much higher than female rates (2) and that females often present with later stage and higher grade lesions (8, 15, 57–59), the observed disparity in survival may partly be due to diagnostic misclassification. For example, when presenting with similar symptoms, males may be more readily referred for cystoscopy than women (60).

Cancers of the anus, anal canal and anorectum show the opposite pattern to urinary bladder; these cancers are more common in females, yet males have lower rates of five-year survival. One hypothesis is that men may be more likely than women to have anus, anal canal and anorectum tumors caused by HIV infection (61), and that such tumors may be more aggressive (25).

Cancer of the tongue was unique, in that adjustment for stage and grade changed the HR estimate from indicating a higher risk of death in males to indicating a higher risk of death in

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females, in the five-years following diagnosis. These unusual observations are difficult to explain, mainly because the etiopathogenesis of this cancer is poorly understood (62, 63).

Strengths of this study include the use of a large, population-based cancer registry database. In addition, SEER has extensive quality control procedures (64, 65). Limitations of this analysis include use of cause of death extracted from death certificates which is known to have problems and imperfections (66). However, inaccuracies are likely to be non-differential by sex. Other limitations include lack of information on co-morbidities and only having adjusted for stage and grade, which may be suboptimal for certain cancers. Lastly, although we utilized the largest US dataset currently available for cancer survival analyses, our results are not perfectly generalizable to the total US population due to the fact that the data are restricted to the 17 cancer registries currently in SEER (18).

In conclusion, this analysis shows that male cancer mortality rates were higher than equivalent female rates for a majority of cancers and these differences largely mirror sex differences in cancer incidence. This analysis also demonstrates modestly, but appreciably, worse survival in men for a number of cancers. Future analytical studies should focus upon the etiological factors responsible for the systematically higher cancer incidence rates among men.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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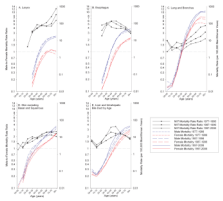

Figure 1.
Male-To-Female Mortality Rate Ratios and Sex-Specific Mortality Rates by Age for Selected Cancers, 1977–2006.
a. Larynx
b. Esophagus
c. Lung and bronchus
d. Skin excluding basal and squamous
e. Liver and intrahepatic bile duct

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Table 1

Sex-Specific Mortality Rates and Male-to-Female Mortality Rate Ratios by Cancer, SEER 9, 1977–2006

Site	Cancer mortality per 100,000 man/woman years						Male-to-female MRR (95% CI)			
	1977–1986		1987–1996		1997–2006					
	male	female	male	female	male	female	1977–1986	1987–1996	1997–2006	1977–2006
All Malignant Cancers	271.93	167.12	275.03	173.52	240.33	162.06	1.63	1.58	1.48	1.56 (1.56–1.56)
All Malignant Cancers excluding Sex-specific	237.63	147.72	236.63	155.67	211.38	145.57	1.61	1.52	1.45	1.52 (1.52–1.52)
All Malignant Cancers excluding Sex-specific and Breast	237.31	115.48	236.30	123.81	211.06	119.89	2.05	1.91	1.76	1.89 (1.89–1.89)
Lip	0.15	0.02	0.08	0.01	0.04	0.01	7.54	5.11	3.88	5.51 (5.05–6.03)
Tongue	1.43	0.52	1.14	0.45	0.94	0.39	2.76	2.51	2.39	2.53 (2.49–2.58)
Salivary Gland	0.45	0.21	0.42	0.18	0.37	0.15	2.20	2.34	2.43	2.32 (2.25–2.39)
Floor of Mouth	0.36	0.11	0.19	0.07	0.08	0.03	3.31	2.62	2.60	2.89 (2.77–3.03)
Gum and Other Mouth	1.04	0.47	0.79	0.41	0.54	0.32	2.20	1.93	1.70	1.92 (1.88–1.96)
Nasopharynx	0.47	0.19	0.42	0.17	0.33	0.13	2.52	2.48	2.44	2.47 (2.40–2.55)
Tonsil	0.52	0.16	0.38	0.12	0.34	0.09	3.19	3.17	3.59	3.28 (3.17–3.39)
Oropharynx	0.34	0.11	0.35	0.12	0.33	0.11	3.20	2.96	3.06	3.05 (2.95–3.16)
Hypopharynx	0.54	0.11	0.36	0.08	0.21	0.05	4.69	4.44	4.44	4.47 (4.30–4.65)
Esophagus	6.56	1.80	7.29	1.80	7.76	1.75	3.64	4.04	4.43	4.08 (4.05–4.11)
Stomach	10.34	4.90	8.39	3.93	6.02	3.04	2.11	2.14	1.98	2.07 (2.06–2.08)
Small Intestine	0.48	0.32	0.51	0.33	0.47	0.31	1.49	1.54	1.50	1.51 (1.47–1.55)
Colon and Rectum	33.13	23.83	29.44	20.15	23.56	16.47	1.39	1.46	1.43	1.42 (1.41–1.42)
Anus, Anal Canal and Anorectum	0.10	0.13	0.14	0.18	0.15	0.20	0.75	0.81	0.77	0.78 (0.75–0.81)
Liver and Intrahepatic Bile Duct	4.14	2.04	5.58	2.56	7.14	3.06	2.03	2.18	2.33	2.23 (2.22–2.25)
Gallbladder	0.78	1.44	0.60	1.07	0.50	0.84	0.54	0.56	0.59	0.56 (0.55–0.57)
Other Biliary	1.18	0.88	0.91	0.65	0.63	0.47	1.33	1.38	1.34	1.34 (1.32–1.37)
Pancreas	13.12	8.96	12.45	9.22	12.26	9.26	1.46	1.35	1.32	1.37 (1.36–1.38)
Retroperitoneum	0.24	0.16	0.14	0.10	0.10	0.07	1.53	1.35	1.38	1.42 (1.37–1.48)
Peritoneum, Omentum and Mesentery	0.10	0.10	0.09	0.14	0.05	0.31	1.00	0.64	0.16	0.39 (0.38–0.41)
Nose, Nasal Cavity and Middle Ear	0.35	0.17	0.27	0.15	0.22	0.12	2.06	1.82	1.87	1.91 (1.84–1.97)
Larynx	3.21	0.51	2.97	0.57	2.41	0.50	6.34	5.25	4.82	5.37 (5.29–5.45)
Lung and Bronchus	85.59	25.94	87.77	37.59	74.08	40.81	3.30	2.33	1.82	2.31 (2.31–2.32)

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Site	Cancer mortality per 100,000 man/woman years						Male-to-female MRR (95% CI)			
	1977–1986		1987–1996		1997–2006		1977–1986	1987–1996	1997–2006	1977–2006
	male	female	male	female	male	female				
Trachea, Mediastinum and Other Respiratory Organs	0.30	0.13	0.19	0.10	0.12	0.06	2.36	2.03	1.95	2.13 (2.04–2.22)
Bones and Joints	0.73	0.43	0.58	0.37	0.55	0.35	1.68	1.59	1.55	1.60 (1.57–1.63)
Soft Tissue including Heart	1.35	1.10	1.57	1.32	1.49	1.20	1.22	1.20	1.24	1.22 (1.21–1.24)
Skin excluding Basal and Squamous	4.70	2.31	5.39	2.32	5.32	2.17	2.04	2.32	2.45	2.30 (2.28–2.32)
Urinary Bladder	8.95	2.62	7.92	2.37	7.59	2.27	3.41	3.35	3.34	3.36 (3.34–3.39)
Kidney and Renal Pelvis	5.57	2.54	6.13	2.84	6.05	2.75	2.19	2.16	2.20	2.19 (2.17–2.20)
Ureter	0.20	0.10	0.18	0.09	0.15	0.09	1.89	1.97	1.74	1.86 (1.78–1.94)
Eye and Orbit	0.16	0.12	0.13	0.09	0.10	0.07	1.33	1.39	1.41	1.36 (1.30–1.42)
Brain and Other Nervous System	5.45	3.64	5.84	3.94	5.45	3.64	1.50	1.48	1.50	1.49 (1.48–1.50)
Endocrine System	0.78	0.83	0.77	0.76	0.80	0.76	0.94	1.01	1.05	1.01 (0.99–1.02)
Lymphoma	9.07	6.12	10.95	7.19	10.28	6.64	1.48	1.52	1.55	1.52 (1.52–1.53)
Myeloma	4.21	2.82	4.82	3.19	4.63	3.10	1.49	1.51	1.50	1.50 (1.49–1.51)
Leukemia	10.92	6.30	10.63	6.10	10.03	5.69	1.73	1.74	1.76	1.75 (1.74–1.76)

Underlying mortality data provided by NCHS (www.cdc.gov/nchs).

Rates are per 100,000 and age-adjusted to the 2000 US Std Population (single ages to 84 - Census P25-1130) standard

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Table 2

Cox Proportional Hazards Regression Models Estimating Male-to-Female Hazard Ratios for Cancer-Specific Death in the Five-Year Period Following Cancer Diagnosis, SEER 17, 1973–2006

Site	Cox Proportional Hazards Models														
	Adjusted for Age					Adjusted for Age and Stage					Adjusted for Age, Stage and Grade				
	N	Deaths	HR	95% CI	P value	N	Deaths	HR	95% CI	P value	N	Deaths	HR	95% CI	P value
Lip	9,280	154	0.91	0.61 – 1.34	0.618	8,460	131	0.89	0.58 – 1.36	0.593	5,538	97	0.93	0.55 – 1.56	0.778
Tongue	20,585	4,690	1.07	1.00 – 1.14	0.036	19,332	4,307	0.92	0.86 – 0.98	0.010	15,577	3,476	0.89	0.83 – 0.95	0.001
Salivary Gland	9,661	1,419	1.52	1.37 – 1.70	<0.001	8,960	1,281	1.27	1.13 – 1.42	<0.001	-	-	-	- -	-
Floor of Mouth	6,879	608	1.35	1.13 – 1.62	0.001	6,386	553	1.29	1.07 – 1.57	0.008	5,069	453	1.32	1.07 – 1.63	0.010
Gum and Other Mouth	12,788	1,725	1.19	1.08 – 1.31	0.000	11,488	1,486	1.14	1.03 – 1.27	0.014	8,740	1,154	1.05	0.93 – 1.18	0.437
Nasopharynx	6,671	1,814	1.17	1.05 – 1.29	0.003	6,170	1,664	1.11	0.99 – 1.23	0.068	4,509	1,251	1.10	0.97 – 1.25	0.125
Tonsil	11,164	1,394	1.13	1.00 – 1.27	0.060	10,592	1,286	1.07	0.94 – 1.22	0.293	8,684	1,014	1.06	0.91 – 1.22	0.468
Oropharynx	2,501	246	0.96	0.73 – 1.26	0.754	2,291	205	1.03	0.76 – 1.40	0.841	1,763	150	1.02	0.71 – 1.45	0.934
Hypopharynx	6,924	1,081	1.00	0.87 – 1.15	0.982	6,621	1,024	1.01	0.87 – 1.17	0.894	5,325	824	0.98	0.84 – 1.16	0.832
Esophagus	36,962	25,493	1.08	1.05 – 1.11	<0.001	30,217	20,644	1.05	1.01 – 1.08	0.006	24,065	16,527	1.05	1.01 – 1.09	0.011
Stomach	76,687	43,115	1.04	1.02 – 1.06	<0.001	67,514	37,645	1.00	0.98 – 1.02	0.964	51,754	28,889	1.01	0.98 – 1.03	0.513
Small Intestine	11,539	2,207	1.22	1.12 – 1.33	<0.001	10,751	2,029	1.25	1.14 – 1.36	<0.001	-	-	-	- -	-
Colon and Rectum	414,964	138,305	1.08	1.07 – 1.09	<0.001	391,548	127,303	1.08	1.06 – 1.09	<0.001	320,549	100,990	1.08	1.07 – 1.10	<0.001
Anus, Anal Canal and Anorectum	10,297	995	1.07	0.94 – 1.22	0.318	9,215	856	1.10	0.95 – 1.27	0.194	6,203	598	1.21	1.02 – 1.43	0.031
Liver and Intrahepatic Bile Duct	41,809	25,735	1.16	1.13 – 1.19	<0.001	33,085	19,555	1.17	1.13 – 1.20	<0.001	-	-	-	- -	-
Gallbladder	11,305	6,168	0.99	0.93 – 1.04	0.639	10,802	5,882	0.97	0.91 – 1.03	0.281	7,430	4,005	1.01	0.94 – 1.09	0.806
Other Biliary	13,017	3,355	0.98	0.91 – 1.05	0.531	10,541	2,589	1.03	0.95 – 1.11	0.453	-	-	-	- -	-
Pancreas	92,133	74,979	1.07	1.05 – 1.08	<0.001	78,100	63,331	1.05	1.03 – 1.07	<0.001	-	-	-	- -	-
Retroperitoneum	3,916	437	1.34	1.11 – 1.62	0.003	3,511	354	1.29	1.04 – 1.59	0.020	-	-	-	- -	-
Nose, Nasal Cavity and Middle Ear	5,949	1,094	1.19	1.05 – 1.34	0.006	4,533	756	1.20	1.03 – 1.39	0.016	-	-	-	- -	-
Larynx	31,755	6,197	1.00	0.94 – 1.07	0.999	25,041	5,263	1.04	0.97 – 1.12	0.217	19,611	4,275	1.09	1.00 – 1.17	0.037
Lung and Bronchus	506,173	365,361	1.19	1.19 – 1.20	<0.001	346,725	242,451	1.17	1.16 – 1.18	<0.001	-	-	-	- -	-
Trachea, Mediastinum and Other Respiratory Organs	2,105	277	1.34	1.02 – 1.77	0.036	1,445	211	1.24	0.90 – 1.70	0.182	-	-	-	- -	-
Bones and Joints	8,977	2,018	1.26	1.15 – 1.38	<0.001	8,069	1,810	1.13	1.03 – 1.24	0.012	-	-	-	- -	-

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Site	Cox Proportional Hazards Models														
	Adjusted for Age					Adjusted for Age and Stage					Adjusted for Age, Stage and Grade				
	N	Deaths	HR	95% CI	P value	N	Deaths	HR	95% CI	P value	N	Deaths	HR	95% CI	P value
Soft Tissue including Heart	24,690	4,934	1.08	1.02 – 1.15	0.005	22,605	4,426	1.10	1.03 – 1.16	0.003	-	-	-	- -	-
Skin excluding Basal and Squamous	140,700	13,309	1.81	1.75 – 1.88	<0.001	132,910	11,881	1.58	1.52 – 1.64	<0.001	-	-	-	- -	-
Urinary Bladder	143,334	23,826	0.73	0.71 – 0.75	<0.001	137,323	22,112	0.85	0.82 – 0.87	<0.001	124,971	19,928	0.83	0.81 – 0.86	<0.001
Kidney and Renal Pelvis	86,116	25,294	1.12	1.09 – 1.15	<0.001	81,740	23,326	0.96	0.93 – 0.99	0.003	-	-	-	- -	-
Ureter	2,588	489	0.90	0.75 – 1.07	0.230	2,356	439	1.06	0.87 – 1.28	0.557	2,002	344	1.17	0.94 – 1.45	0.168
Eye and Orbit	7,422	482	1.09	0.91 – 1.31	0.331	6,494	411	1.06	0.87 – 1.29	0.573	-	-	-	- -	-
Brain and Other Nervous System	63,256	34,104	1.13	1.10 – 1.15	<0.001	-	-	-	- -	-	-	-	-	- -	-
Endocrine System	74,540	4,043	1.86	1.75 – 1.99	<0.001	72,112	3,704	1.32	1.24 – 1.42	<0.001	-	-	-	- -	-
Lymphoma	178,638	48,517	1.20	1.18 – 1.22	<0.001	-	-	-	- -	-	-	-	-	- -	-
Myeloma	47,306	23,136	1.03	1.01 – 1.06	0.015	-	-	-	- -	-	-	-	-	- -	-
Leukemia	104,012	41,695	1.04	1.02 – 1.06	<0.001	-	-	-	- -	-	-	-	-	- -	-

All Cox proportional hazards models were adjusted for year of diagnosis (categorical: 1973–1979, 1980–1986, 1987–1993, 1994–2000, 2001–2006). Abbreviations: CI, confidence interval; HR, hazard ratio. “-” Stage and/or grade information was available for less than 60% of cases included in the age-adjusted model.