TITLE

Sex differences in cancer incidence and survival: a pan-cancer analysis

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RUNNING TITLE

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The authors do not have any conflicts of interests with this study.

LIST OF ABBREVIATIONS USED

CBTRUS: Central Brain Tumor Registry of the United States

CDC: Centers for Disease Control and Prevention

CI: Confidence Interval

HR: Hazard ratio

ICD-O-3: International Classification of Disease for Oncology. Third Edition

IRR: Incidence rate ratio

NPCR: National Program of Cancer Registries

NCI: National Cancer Institute

SEER: Surveillance, Epidemiology, and End Results

USCS: United States Cancer Statistics

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Abstract

Background: Sex plays an important role in the incidence, prognosis, and mortality of cancers, but often is not considered in disease treatment.

Methods: We quantified sex differences in cancer incidence using the USCS public use database and sex differences in cancer survival using SEER public use data from 2001 to 2016. Age-adjusted male-to-female incidence rate ratios with 95% CIs were generated by primary cancer site, race, and age groups. Additionally, age-adjusted hazard ratios with 95% CI by sex within site were generated.

Results: In general, cancer incidence and overall survival was lower in males than females, with Kaposi sarcoma (IRR: 9.751, 95% CI: 9.287-10.242, p<0.001) having highest male-to-female incidence, and thyroid cancers (HR: 1.774; 95% CI: 1.707-1.845) having largest male-to-female survival difference. Asian or Pacific Islanders had particularly high male-to-female incidence in larynx cancers (IRR: 8.199; 95% CI: 7.203-9.363; p<0.001), relative to other races. Among primary brain tumors, germ cell tumors had the largest male-to-female incidence (IRR: 3.03; 95% CI: 2.798-3.284, p<0.001).

Conclusions:

Overall, incidence and survival of cancer vary significantly by sex, with males generally having lower incidence and survival compared to females. Male-to-female incidence differences were also noted across race and age groups. These results provide strong evidence that the fundamental biology of sex differences affects cancers of all types.

Impact: This study represents the most recent and comprehensive reporting of sex differences in cancer incidence and survival in the United States. Identifying disadvantaged groups is critical as it can provide useful information to improve cancer survival, as well as to better understand the etiology and pathogenesis of specific cancers.

Introduction

Sex plays an important role in the incidence, prognosis, and mortality of numerous cancers[1] but is often not taken into consideration in the treatment of the disease. While the reasons behind sex differences in cancer incidence and survival are not well understood, recent studies have suggested that genetic and environmental factors, and their complex interactions, may contribute to sex differences, specifically to the worse overall prognosis for males compared to females.[1-3] Prior research suggests that males have a higher incidence of cancer[1, 4], and recent studies in Europe[5], Korea[6], Canada[7], and Australia[8] have consistently reported that males are less likely to survive a diagnosis of cancer. Identifying disadvantaged groups is critical as it can provide useful information to improve cancer survival, as well as to better understand the etiology and pathogenesis of specific cancers.

Few large-scale studies have systematically examined sex differences in incidence and survival across all cancers. Many of these studies are older and use smaller, less comprehensive datasets[4, 9]. A recently published study used the Centers for Disease Control and Prevention's (CDC) National Program of Cancer Registries (NPCR) and the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) Program datasets to examine incidence rates by sex of cancers diagnosed from 2011 to 2015 and death rates by sex of cancers diagnosed from 2012 to 2016[10]. However, this analysis was limited to patients between 20 and 49 years of age. Age is the most significant factor reported in cancer incidence and survival[2], and the risk of being diagnosed with cancer significantly increases in adults older than 50 years.

The purpose of this study was to use current population-based data to quantify differences in cancer incidence and survival by sex that was comprehensive for both age and race. In this study, we investigated sex differences in cancer incidence among those ages 0-85+ years from 2001 to 2016 using data from the United States Cancer Statistics (USCS) public use database, and for sex differences in cancer survival using the SEER dataset (2001-2016). Datasets were age-adjusted and only included diagnostically-confirmed primary, malignant tumors from 2001 to 2016, resulting in a sample population of about 11.4 million for incidence and 2.9 million for survival. In addition, given the interests of our group, we examined sex differences in incidence and survival for specific brain tumor histologies[3, 11-13]. Identifying the role of sex in cancer incidence and survival may improve outcomes by providing healthcare professionals additional insight regarding sex-specific approaches to treatment.

Material & Methods

Cancer incidence data

Population-based cancer incidence data by primary site, sex, race, and age groups were obtained from the USCS public-use database, which combines data from the CDC's NPCR dataset and the NCI's SEER Program dataset. The USCS dataset includes de-identified cancer incidence data from central cancer registries (state)

reported to NPCR from 46 states and the District of Columbia, and from SEER for 4 states, and represents 99.9% of the US population (cases diagnosed in Mississippi from 2001-2002 were not available).

Survival data

Survival data by primary site and sex were obtained from the NCI SEER 18 registries which represents approximately 28% of the United States (US) population.

Study Cohort

Cases were classified according to the *International Classification of Diseases for Oncology, Third Edition*.(14) Primary site and histology groupings were classified by the site recode ICD-O-3/WHO 2008 definition provided by SEER. Only those with a malignant behavior code (/3) were kept for all analyses. For brain-specific analyses, histology groupings were defined by the Central Brain Tumor Registry of the United States (CBTRUS) Brain and Other Central Nervous System Tumor Histology Groupings, and primary sites C71.0-C72.5, C72.8-C72.9, C70.0-C70.9, C75.1-C75.3, and C30.0..[(15)] Data were restricted to patients with primary, first sequence tumors diagnosed between 2001 and 2016. Only diagnostically confirmed cases (microscopically or radiographically) were included. Sex-specific cancers (e.g. cervical, ovarian, and prostate) were excluded.

Self-reported race categories included in this study were White, Black, American Indian/Alaska Native (AIAN), and Asian/Pacific Islander (API). Other race, unspecified, and unknown race were included in analyses that were not race-specific. Age at diagnosis groups used in this analysis were 0-14, 15-39, 40-64, and 65 years and older. For brain- specific analyses, histology groupings were defined by the Central Brain Tumor Registry of the United States (CBTRUS) Brain and Other Central Nervous System Tumor Histology Groupings, and primary sites C71.0-C72.5, C72.8-C72.9, C70.0-C70.9, C75.1-C75.3, and C30.0..[(15)] Counts are not presented when fewer than 16 cases were reported for any specific site.

Data were collected from January 1, 2001 to December 31, 2016. Data analysis took place from June 18 to July 1, 2019.

Statistical Analysis

Incidence rate ratios (IRR) with 95% confidence intervals (95% CI) were generated to compare male-to-female incidence across all cancers using the SEER*Stat software, version 8.3.5. IRRs were calculated by sex, sex and race, and sex and age at diagnosis. All rates were age-adjusted and standardized to the 2000 US population (19 age groups – Census P25-1130) to adjust for differences in age distribution.[(16)] 95% CI were calculated using the method described in Tiwari et al.[(17)] Cox proportional hazard models were used to calculate male-to-female hazard ratios (HR) adjusted for age in R 3.6.0. Statistical significance was set at $P < 0.05$.

Results

Incidence was calculated for 14,281,801 patients (6,423,073 male [45.0%] and 7,858,728 female [55.0%]) diagnosed with cancer from 2001 to 2016 (Supplemental Table 1). Incidence rate ratios [IRR] were calculated by sex (Supplemental Table 1), sex and race (Supplemental Table 2), and sex and age (Supplemental Table 3). Survival analyses were conducted on 3,705,584 patients (1,654,454 male [44.6%] and 2,051,130 female [55.4%]).

Overall, males had lower cancer incidence (IRR: 0.958; 95% CI: 0.957-0.959, p<0.001) but worse survival (HR: 1.568; 95% CI: 1.564-1.573, p<0.001) compared to females (Supplemental Table 1 and Supplemental Table 4).

Overall Incidence

Figure 1 and Table 1 depict age-standardized male-to-female incidence rate ratios from 2001 to 2016 for all major cancer sites and groupings. Highest male incidence rate ratios were exhibited in Kaposi sarcoma (IRR: 9.751; 95% CI: 9.287-10.242, p<0.001), larynx (IRR: 4.567; 95% CI: 4.511-4.624, p<0.001), mesothelioma (IRR: 4.112; 95% CI: 4.011-4.216, p<0.001), and liver (IRR: 3.381; 95% CI: 3.349-3.412, p<0.001).

Females exhibited higher incidence of cancer in breast (IRR: 0.010; 95%: CI: 0.093, 0.103, p<0.001), peritoneum, omentum and mesentery (IRR: 0.098; 95%: CI: 0.093, 0.103, p<0.001), thyroid (IRR: 0.313; 95% CI: 0.311-0.315, p<0.001), gallbladder (IRR: 0.543; 95% CI: 0.532-0.554, p<0.001), anus, anal canal and anorectum (IRR:0.683; 95% CI: 0.672-0.693, p<0 .001), and appendix (IRR:0.900; 95% CI: 0.883-0.919, p<0.001).

Race Stratified Incidence

Figure 2 shows age-adjusted male-to-female incidence rate ratios from 2001 to 2016 for all major cancer site groupings stratified by race. Across all sites, the male-to-female IRR was highest in whites (IRR: 0.955; 95% CI: 0.954-0.956, p<0.001) and lowest in American Indians or Alaska Natives (IRR: 0.924; 95% CI: 0.919-0.930, p<0.001) (Supplemental Table 2). For cancers of the anus, anal canal and anorectum, females had higher incidence compared to males for whites (IRR:0.628; 95% CI: 0.617-0.638, p<0.001), American Indians or Alaska Natives (IRR:0.721; 95% CI: 0.575-0.901, p=0.004), and Asians or Pacific Islanders (IRR:0.774; 95% CI: 0.671-0.891, p<0.001), while males had higher incidence among blacks (IRR: 1.107; 95% CI: 1.058-1.158, p<0.001). Asian or Pacific Islander males exhibited particularly high incidence in larynx cancers (IRR: 8.199; 95% CI: 7.203-9.363; p<0.001) compared to whites (IRR: 4.443; 95% CI: 4.383-4.503, p<0.001), blacks (IRR: 5.123; 95% CI: 4.957-5.296, p<0.001), and American Indians or Alaska Natives (IRR: 4.530; 95% CI: 3.809-5.414, p<0.001).

Age Stratified Incidence

Across site, cancer incidence was higher for females ages 15-39 and 65 and older, and higher for males ages 0-14 and 40-64. (Supplemental Table 3). Male-to-female IRRs were highest in children aged 0-14 years (IRR: 1.125; 95% 1.113-1.136, p<0.001). The incidence rate ratio for appendix cancers was higher in females age groups 0-14, 15-39, and 40-64 years but higher in males 65 years or older (IRR: 1.087; 95% CI: 1.047-1.129, p<0.001). Higher incidence of pancreas cancer was exhibited in females ages 0-14 years (IRR: 0.574; 95% CI:

0.417-0.786, p<0.001) and 15-39 years (IRR: 0.944; 95% CI: 0.897-0.993, p=0.03), whereas males expressed higher incidence in the 40 to 64 years (IRR: 1.476; 95% CI: 1.460-1.492 p<0.001) and 65 years or older (IRR: 1.17; 95% CI: 1.16-1.18, p<0.001) age groups. Similarly, in melanomas of the skin, incidence was higher in females ages 0-14years (IRR: 0.912; 95% CI: 0.832-0.999, p=0.05) and 15-39 years (IRR: 0.579; 95% CI: 0.572-0.586, p<0.001), and higher in males ages 40-64 years (IRR:1.248; 95% CI: 1.24-1.256, p<0.001) and 65 years or older (IRR: 2.319; 95% CI: 2.302-2.336, p<0.001). Male-to-female incidence of trachea, mediastinum, and other respiratory organs cancers was highest in the 15-39 age group (IRR: 7.051; 95% CI: 6.171-8.085, p<0.001). Kidney and renal pelvis cancers were characterized with higher incidence in males in all age groups except 0-14 years (IRR: 0.864; 95% CI: 0.828-0.902, p<0.001). Incidence of mesothelioma in males was lowest in the 15-39 age group (IRR: 0.801; 95% CI: 0.685-0.935, p=0.005) and highest in adults 65 years or older (IRR: 5.160; 95% CI: 5.005-5.32, p<0.001). Incidence of Kaposi sarcoma in males was lowest in the 65 years or older age group (IRR: 3.048; 95% CI: 2.846-3.265, p<0.001), compared to IRRs of 22.935 and 19.924 in ages 15-39 and 40-50, respectively.

Survival

Figure 3 shows age-adjusted male-to-female hazard ratios from 2001 to 2016 for all major cancer site groupings. Males experienced better overall survival in Kaposi sarcoma (HR: 9.751; 95% CI: 9.287-10.242, p<0.001), other lymphocytic leukemia (HR: 0.812; 95% CI: 0.721-0.914, p<0.001), cancers of the larynx (HR: 0.926; 95% CI: 0.894-0.960, p<0.001), and oropharynx (HR: 0.878; 95% CI: 0.800-0.964, p=0.01), despite having a higher incidence compared to females in those specific cancers (Supplemental Table 4). Females were observed to have better overall survival in most other cancers, particularly cancers of the thyroid (HR: 1.773; 95% CI: 1.707-1.845, p<0.001), salivary gland (HR: 1.610; 95% CI: 1.515-1.712, p<0.001), breast (HR: 1.540; 95% CI: 1.474-1.610, p<0.001), anus, anal canal and anorectum (HR:1.488; 95% CI: 1.421-1.558, p<0.001), melanoma of the skin (HR: 1.410; 95% CI: 1.383-1.437, p<0.001).

Males had significantly lower incidence and worse survival compared to females in cancers of the thyroid (IRR: 0.313; HR: 1.773), breast (IRR: 0.010; HR: 1.540), gallbladder (IRR: 0.543; HR: 1.066), anus, anus canal and anorectum (IRR: 0.683; HR: 1.488), and cranial nerves and other nervous system (IRR: 0.956; HR: 1.434) (Supplemental Table 1 and Supplemental Table 4). There are no sites in which males had lower incidence and better survival. Incidence was higher for males in all four sites that males experienced better overall survival (Kaposi sarcoma, other lymphocytic leukemia, larynx, and oropharynx cancers).

Brain-Specific Analyses

Given our group's research focus in sex differences in brain tumors, we performed additional analyses on specific malignant brain tumor histologies (Figures 4 and 5, Supplemental Table 4 and 5)[11-13, 15]. Among these, males had the highest incidence rate ratio of germ cell tumors (IRR: 3.03; 95% CI: 2.798-3.284, p<0.001), hematopoietic neoplasms (IRR: 1.842; 95% CI: 1.540-2.206, p<0.001), and glioblastoma (IRR: 1.554; 95% CI =

1.537-1.570, p<0.001). Females had higher incidence than males among other neuroepithelial tumors (IRR: 0.425; 95% CI: 0.305-0.587, p<0.001) and malignant meningioma (IRR: 0.731; 95% CI: 0.687-0.777, p<0.001). Males had shorter survival among nerve sheath tumors (HR: 2.739; 95% CI: 1.589-4.720, p<0.001), neoplasms related to the meninges (HR: 1.859; 95% CI: 1.072-3.223, p=0.03), and malignant meningioma (HR: 1.488; 95% CI: 1.260-1.757, p<0.001). Females only exhibited shorter survival among germ cell tumors (HR: 0.720; 95% CI: 0.526-0.985, p= 0.04).

Discussion

Using data representative of 99.9% of the US population for incidence and data from approximately 28% of the population for survival, this analysis of cancer incidence and survival across a 15-year period identified significant differences by sex. Males had significantly higher incidence and worse survival outcomes in the majority of cancer sites, consistent with what has been previously reported.[1, 10] There was further variation of incidence rates by age groups, with females ages exhibiting higher cancer incidence than males in the 15-39 years age group. The male-to-female IRR was similar among all examined race groups.

Sex disparities in cancer incidence and survival can be attributed to behavioral and environmental factors as well as biological differences. Higher incidence and worse survival in males can be partially attributed to increased tobacco use(18) compared to females and increased exposure to oncogenic agents such as oral HPV.[19] Males have also been found to be more likely to engage in high-risk behaviors and less likely to utilize health care services than females. Occupational exposures to carcinogens such as asbestos may influence sex differences in incidence and survival. Sex differences in immune system functions[20], along with genetic and hormonal differences[21], are also likely to play a role in the observed sex disparities.

Previous analyses have found that, in contrast to other cancers, females are more likely to be diagnosed with melanoma than males until age 40 years.[22] This pattern was present in the incidence analyses of this study, as the male-to-female incidence rate ratio was less than 1 for the age groups 0-14 and 15-39 years, and more than 1 for age 40-59 and 60 years or older. Numerous studies suggest that the increased incidence of melanoma in adolescent and young adult women is influenced by the increased usage of indoor tanning facilities.[23] Male hormones and physiological sex differences are possible factors that may contribute to the higher overall male incidence of skin and other cancers.[24]

Based on our findings, men have significantly lower incidence, but worse survival, for breast cancer. These results are supported by previous studies that have found similar trends[25, 26]. These studies noted that the majority of male breast cancer cases are associated with *BRCA2* mutations, as well as Klinefelter syndrome.

Studies have also noted that a lack of screening and early detection, and the impact this has on stage migration, contributes to these lower survival outcomes[27].

In this study, thyroid cancers were observed to have lower incidence and worse survival in males compared to females. There have been few molecular explanations for sex differences in thyroid cancers, though estrogen receptors may have an important role.[21, 28] Other studies have suggested that a substantial percentage of thyroid cancer diagnoses could be due to factors such as obesity and smoking. Higher female incidence may be influenced by recent advances in thyroid cancer detection, possibly contributing to over-diagnosis and overtreatment of female patients relative to male patients.[24, 28, 29]

Kaposi sarcoma had the highest male-to-female incidence rate ratio and the lowest female survival in this analysis. A recent study found that despite advances in treatment, HIV-infected persons have an 800-fold elevated risk of Kaposi sarcoma relative to the general population.[29] However, male incidence of Kaposi sarcoma has declined considerably since the beginning of the HIV/AIDS epidemic, as evidenced by a similar analysis of SEER data from 1975 to 2004 that exhibited an incidence rate ratio approximately 3 times larger than the ratio calculated in this study. The survival disadvantage for females has not been well-studied in the U.S., but an analysis of the incidence and clinical outcomes of HIV-positive Kaposi sarcoma patients in Uganda suggested that females were more likely to experience more advanced and severe case of Kaposi sarcoma. Delayed diagnosis of Kaposi sarcoma may account for sex differences in survival, though more investigation is necessary as other studies showing similar patterns are over a decade old.[30, 31]

This study identified sex differences in multiple brain tumor histologies, such as germ cell tumors, malignant meningioma, and glioblastoma. Glioblastoma is the most common malignant brain tumor and is also the most fatal. We found males with this tumor had both increased incidence and risk of death. There are not many proven risk factors for this tumor, but previous studies have identified potential sex-related genetic factors related to incidence and survival.[3, 11-13, 32] This study demonstrates the necessity for detailed investigations into these potential differences allowing us to uncover the biological underpinnings of these sex differences thereby helping us to advance treatments that could be tailored for males and females separately.

There are several limitations to this analysis that are worth noting. Survival data were unavailable in the dataset used for incidence analyses, and therefore a subset was used. In addition, the survival analyses were conducted only by sex differences with adjustment for age, and did not assess potential variations in sex difference by race. Furthermore, there may be other variables not considered in this analysis or not available in the datasets used for analysis that could influence sex disparities in cancer incidence and survival, such as screenings, treatments, molecular testing, comorbidities, and risk factors (smoking, obesity, etc.).

To our knowledge, this study represents the most recent comprehensive reporting of cancer incidence and survival by sex in the United States. Cancer registry data for incidence included approximately 99.9% of the U.S. population while SEER survival data represented approximately 28% of the population.[1, 2] Among patients diagnosed with non-sex-specific cancers from 2001 to 2016, males had higher incidence and worse overall survival compared to females in the vast majority of cancer sites. Additionally, male-to-female incidence varied by race and age groups. Further examination is necessary to obtain a better understanding of sex disparities in cancer etiology and prognosis, as well as the clinical implications of observed sex differences.

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Table 1. Frequency and Incidence Rate Ratios[a] by Sex (Males:Females) in SEER Site Recode ICD-O-3/WHO 2008 Sites, 2001-2016, National Program of Cancer Registries and Surveillance, Epidemiology, and End Results SEER*Stat Database: NPCR and SEER Incidence – U.S. Cancer Statistics Public Use Research Database, Nov 2018 Submission (2001-2016).

Cancer Site	Male	Female	% of all tumors	Male-to-female IRR (95% CI)	p-value
All Sites	**6,423,073**	**7,858,728**	**100.00**	**0.958 (0.957-0.959)**	**<0.001**
Oral Cavity and Pharynx	**325,572**	**133,512**	**3.21**	**2.737 (2.719-2.755)**	**<0.001**
Lip	19,697	6,954	0.19	3.509 (3.413-3.608)	<0.001
Tongue	96,457	38,167	0.94	2.797 (2.764-2.831)	<0.001
Salivary Gland	27,450	20,412	0.34	1.573 (1.544-1.602)	<0.001
Floor of Mouth	17,649	7,442	0.18	2.660 (2.588-2.734)	<0.001
Gum and Other Mouth	33,406	26,642	0.42	1.478 (1.454-1.502)	<0.001
Nasopharynx	16,528	6,923	0.16	2.569 (2.497-2.643)	<0.001
Tonsil	71,376	15,215	0.61	5.077 (4.987-5.167)	<0.001
Oropharynx	15,081	4,501	0.14	3.746 (3.622-3.875)	<0.001
Hypopharynx	21,068	5,071	0.18	4.750 (4.605-4.900)	<0.001
Other Oral Cavity and Pharynx	6,860	2,185	0.06	3.577 (3.406-3.757)	<0.001
Digestive System	**1,788,538**	**1,480,610**	**22.89**	**1.454 (1.451-1.457)**	**<0.001**
Esophagus	154,335	40,576	1.36	4.573 (4.523-4.624)	<0.001
Stomach	170,160	106,378	1.94	1.948 (1.933-1.963)	<0.001
Small Intestine	44,550	41,042	0.60	1.270 (1.253-1.287)	<0.001
Colon and Rectum	946,324	893,241	12.88	1.287 (1.284-1.291)	<0.001
Colon excluding Rectum	637,241	666,291	9.13	1.184 (1.180-1.188)	<0.001
Cecum	124,940	159,818	1.99	1.002 (0.995-1.010)	0.60
Appendix	17,855	21,605	0.28	0.900 (0.883-0.919)	<0.001
Ascending Colon	112,188	136,524	1.74	1.054 (1.046-1.063)	<0.001
Hepatic Flexure	30,737	31,554	0.44	1.248 (1.228-1.268)	<0.001
Transverse Colon	53,385	58,828	0.79	1.144 (1.131-1.158)	<0.001
Splenic Flexure	21,483	18,913	0.28	1.392 (1.365-1.420)	<0.001
Descending Colon	40,214	34,793	0.53	1.387 (1.367-1.407)	<0.001
Sigmoid Colon	199,590	167,202	2.57	1.414 (1.405-1.424)	<0.001
Large Intestine, NOS	36,849	37,054	0.52	1.253 (1.234-1.271)	<0.001
Rectum and Rectosigmoid Junction	309,083	226,950	3.75	1.585 (1.576-1.594)	<0.001
Rectosigmoid Junction	79,226	61,989	0.99	1.500 (1.484-1.516)	<0.001
Rectum	229,857	164,961	2.76	1.617 (1.607-1.627)	<0.001
Anus, Anal Canal and Anorectum	26,639	45,251	0.50	0.683 (0.672-0.693)	<0.001
Liver and Intrahepatic Bile Duct	193,301	73,736	1.87	2.973 (2.948-2.999)	<0.001
Liver	179,425	59,981	1.68	3.381 (3.349-3.412)	<0.001
Intrahepatic Bile Duct	13,876	13,755	0.19	1.199 (1.171-1.229)	<0.001
Gallbladder	13,584	31,907	0.32	0.543 (0.532-0.554)	<0.001
Other Biliary	30,666	26,444	0.40	1.445 (1.421-1.469)	<0.001
Pancreas	192,135	185,711	2.65	1.260 (1.252-1.269)	<0.001
Retroperitoneum	7,428	7,998	0.11	1.036 (1.003-1.070)	0.03
Peritoneum, Omentum and Mesentery	1,663	20,377	0.15	0.098 (0.093-0.103)	<0.001
Other Digestive Organs	7,753	7,949	0.11	1.200 (1.163-1.239)	<0.001
Breast	**23,508**	**2,851,892**	**20.13**	**0.010 (0.009-0.010)**	**<0.001**
Respiratory System	**1,301,901**	**1,045,144**	**16.43**	**1.505 (1.501-1.509)**	**<0.001**
Nose, Nasal Cavity & Middle Ear	16,793	11,213	0.20	1.730 (1.688-1.772)	<0.001
Larynx	126,411	31,826	1.11	4.567 (4.511-4.624)	<0.001
Lung and Bronchus	1,153,272	999,509	15.07	1.402 (1.398-1.406)	<0.001
Pleura	588	390	0.01	1.876 (1.645-2.142)	<0.001
Trachea, Mediastinum &Other Respiratory Organs	4,837	2,206	0.05	2.366 (2.248-2.491)	<0.001
Bones and Joints	**21,868**	**17,256**	**0.27**	**1.318 (1.292-1.345)**	**<0.001**
Soft Tissue including Heart	**71,124**	**58,394**	**0.91**	**1.367 (1.352-1.383)**	**<0.001**
Skin excluding Basal and Squamous	**481,029**	**377,954**	**6.01**	**1.432 (1.426-1.438)**	**<0.001**
Melanoma of the Skin	445,071	351,601	5.58	1.414 (1.408-1.420)	<0.001
Other Non-Epithelial Skin	35,958	26,353	0.44	1.684 (1.657-1.711)	<0.001
Urinary System	**1,011,526**	**452,236**	**10.25**	**2.724 (2.714-2.734)**	**<0.001**
Urinary Bladder	610,248	202,626	5.69	3.854 (3.835-3.874)	<0.001
Kidney and Renal Pelvis	386,667	239,613	4.39	1.843 (1.834-1.853)	<0.001
Ureter	9,929	6,953	0.12	1.853 (1.796-1.912)	<0.001
Other Urinary Organs	4,682	3,044	0.05	1.965 (1.876-2.059)	<0.001
Eye and Orbit	**14,918**	**12,109**	**0.19**	**1.380 (1.347-1.414)**	**<0.001**
Brain and Other Nervous System	**158,403**	**126,971**	**2.00**	**1.368 (1.357-1.378)**	**<0.001**
Brain	149,601	117,220	1.87	1.404 (1.393-1.415)	<0.001

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Cancer Site	Male	Female	% of all tumors	Male-to-female IRR (95% CI)	p-value
Cranial Nerves and Other Nervous System	8,802	9,751	0.13	0.956 (0.929-0.985)	0.003
Endocrine System	**138,181**	**417,646**	**3.89**	**0.343 (0.341-0.345)**	**<0.001**
Thyroid	121,823	403,056	3.68	0.313 (0.311-0.315)	<0.001
Other Endocrine including Thymus	16,358	14,590	0.22	1.199 (1.172-1.226)	<0.001
Lymphoma	**481,556**	**412,333**	**6.26**	**1.366 (1.361-1.372)**	**<0.001**
Hodgkin Lymphoma	66,933	55,068	0.85	1.257 (1.243-1.272)	<0.001
Nodal	65,236	53,583	0.83	1.258 (1.244-1.273)	<0.001
Extranodal	1,697	1,485	0.02	1.228 (1.144-1.319)	<0.001
Non-Hodgkin Lymphoma	414,623	357,265	5.40	1.386 (1.379-1.392)	<0.001
Nodal	283,299	238,772	3.66	1.414 (1.406-1.422)	<0.001
Extranodal	131,324	118,493	1.75	1.329 (1.319-1.340)	<0.001
Myeloma	**131,949**	**110,011**	**1.69**	**1.449 (1.437-1.461)**	**<0.001**
Leukemia	**274,944**	**199,359**	**3.32**	**1.606 (1.596-1.615)**	**<0.001**
Lymphocytic Leukemia	147,278	97,378	1.71	1.742 (1.728-1.757)	<0.001
Acute Lymphocytic Leukemia	38,177	28,836	0.47	1.322 (1.302-1.342)	<0.001
Chronic Lymphocytic Leukemia	96,950	64,244	1.13	1.869 (1.850-1.888)	<0.001
Other Lymphocytic Leukemia	12,151	4,298	0.12	3.259 (3.146-3.377)	<0.001
Myeloid and Monocytic Leukemia	118,818	94,672	1.49	1.474 (1.461-1.486)	<0.001
Acute Myeloid Leukemia	73,460	60,754	0.94	1.422 (1.406-1.437)	<0.001
Acute Monocytic Leukemia	4,834	4,051	0.06	1.372 (1.314-1.431)	<0.001
Chronic Myeloid Leukemia	37,340	27,383	0.45	1.596 (1.571-1.622)	<0.001
Other Myeloid/Monocytic Leukemia	3,184	2,484	0.04	1.563 (1.481-1.649)	<0.001
Other Leukemia	8,848	7,309	0.11	1.493 (1.446-1.540)	<0.001
Other Acute Leukemia	4,088	3,199	0.05	1.579 (1.507-1.656)	<0.001
Aleukemic, Subleukemic and NOS	4,760	4,110	0.06	1.424 (1.365-1.486)	<0.001
Mesothelioma	**26,840**	**8,314**	0.85	**4.112 (4.011-4.216)**	**<0.001**
Kaposi Sarcoma	**14,956**	**1,898**	0.83	**9.751 (9.287-10.242)**	**<0.001**

[a] Rates are per 100,000 and age-adjusted to the 2000 US standard population.

Abbreviations: SEER, Surveillance, Epidemiology, and End Results program; NPCR, National Program of Cancer Registries; ICD-O-3/WHO 2008, International Classification of Diseases for Oncology, 3rd Edition, 2000. World Health Organization, Geneva, Switzerland; CI, confidence interval; NOS, not otherwise specified.

Figure Legends

Figure 1. Forest Plot of Incidence Rate Ratios (IRR) by Sex (Males:Females) and SEER Site Recode ICD-O-3/WHO 2008 Major Groupings with 95% Confidence Intervals, 2001-2016. National Program of Cancer Registries and Surveillance, Epidemiology, and End Results SEER*Stat Database: NPCR and SEER Incidence – U.S. Cancer Statistics Public Use Research Database, Nov 2018 Submission (2001-2016). IRRs are plotted on a log scale. Rates are per 100,000 and age-adjusted to the 2000 US standard population.

Figure 2. Forest Plot of Incidence Rate Ratios (IRR) by Sex (Males:Females) and SEER Site Recode ICD-O-3/WHO 2008 Major Groupings Stratified by Race with 95% Confidence Intervals, 2001-2016. National Program of Cancer Registries and Surveillance, Epidemiology, and End Results SEER*Stat Database: NPCR and SEER Incidence – U.S. Cancer Statistics Public Use Research Database, Nov 2018 Submission (2001-2016). IRRs are plotted on a log scale. Rates are per 100,000 and age-adjusted to the 2000 US standard population.

Figure 3. Forest Plot of Hazard Ratios (HR) by Sex (Males:Females) and SEER Site Recode ICD-O-3/WHO 2008 Major Groupings with 95% Confidence Intervals, 2001-2016. SEER*Stat Database: Incidence – SEER 18 Registries + Hurricane Katrina Impacted Louisiana Cases, Nov 2018 Submission (1973-2016 varying). HRs are plotted on a log scale. Rates are adjusted for age at diagnosis.

Figure 4. Forest Plot of Incidence Rate Ratios (IRR) by Sex (Males:Females) and Malignant Brain and other CNS tumor Histologies with 95% Confidence Intervals, 2001-2016.[19] National Program of Cancer Registries and Surveillance, Epidemiology, and End Results SEER*Stat Database: NPCR and SEER Incidence – U.S. Cancer Statistics Public Use Research Database, Nov 2018 Submission (2001-2016). IRRs are plotted on a log scale. Rates are per 100,000 and age-adjusted to the 2000 US standard population.

Figure 5. Forest Plot of Hazard Ratios (HR) by Sex (Males:Females) and Malignant Brain and other CNS tumor Histologies with 95% Confidence Intervals, 2001-2016.[19] SEER*Stat Database: Incidence – SEER 18 Registries + Hurricane Katrina Impacted Louisiana Cases, Nov 2018 Submission (1973-2016 varying). HRs are plotted on a log scale. Rates are adjusted for age at diagnosis.

Figure 1

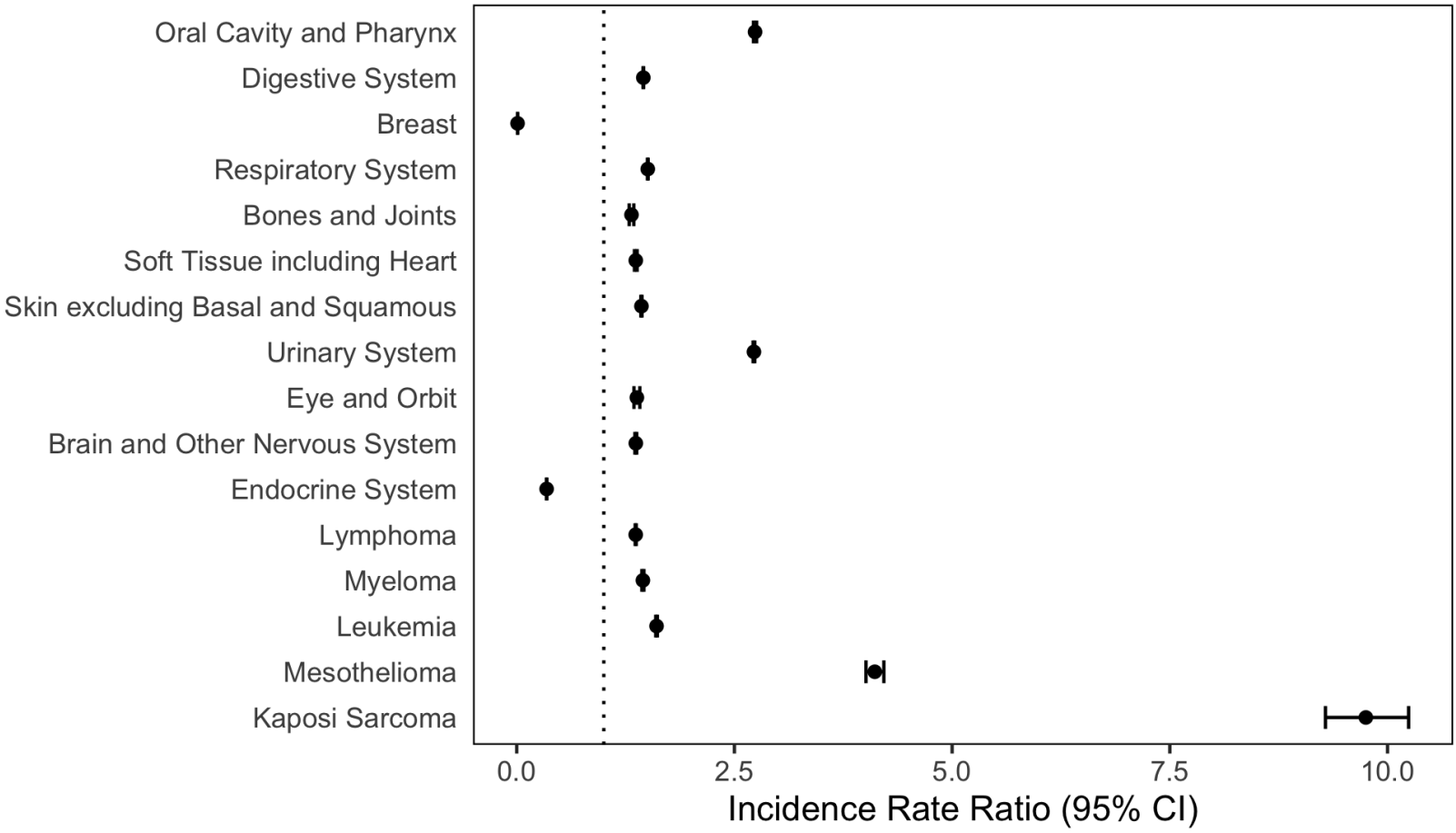

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Figure 2

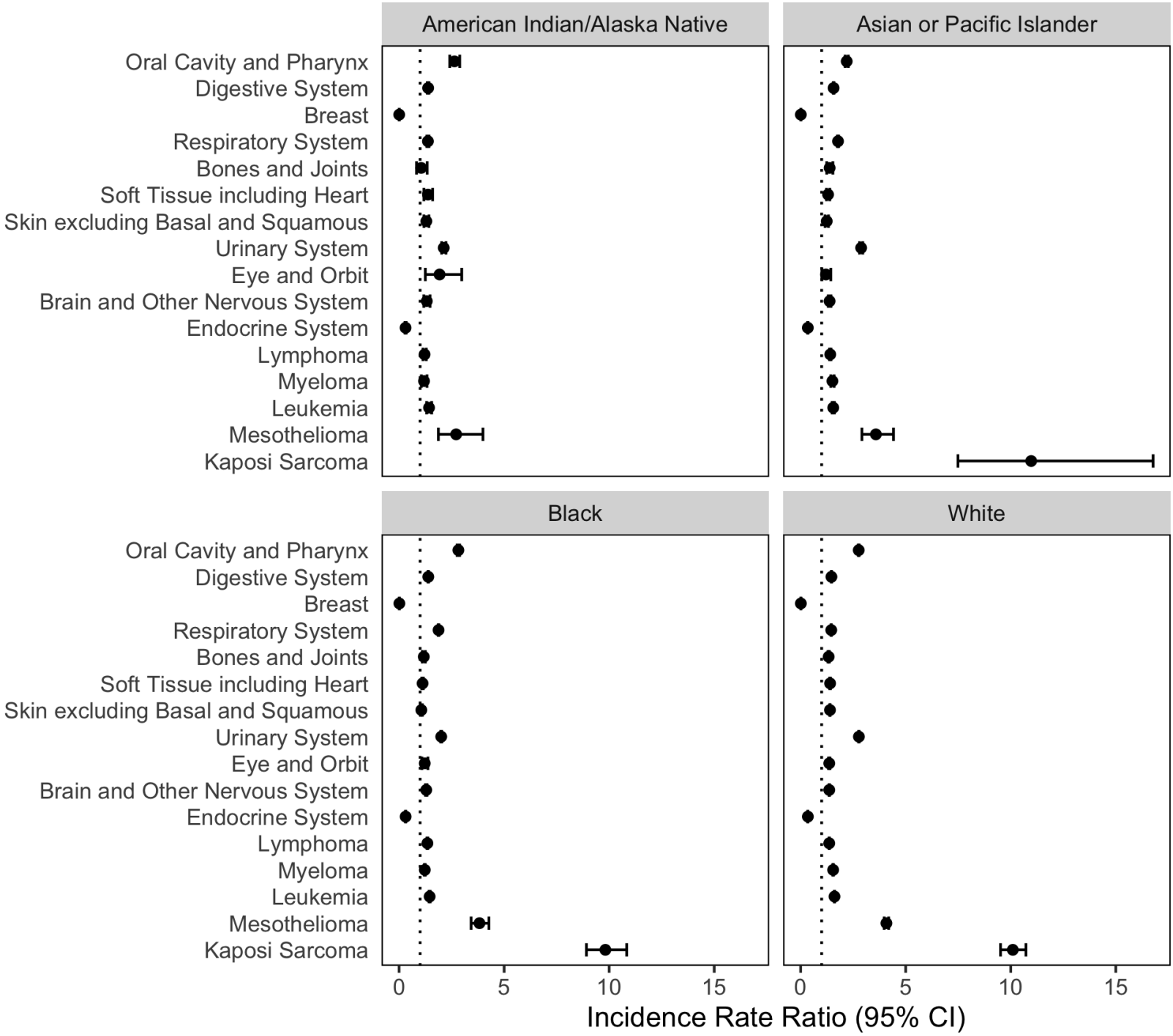

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Figure 3

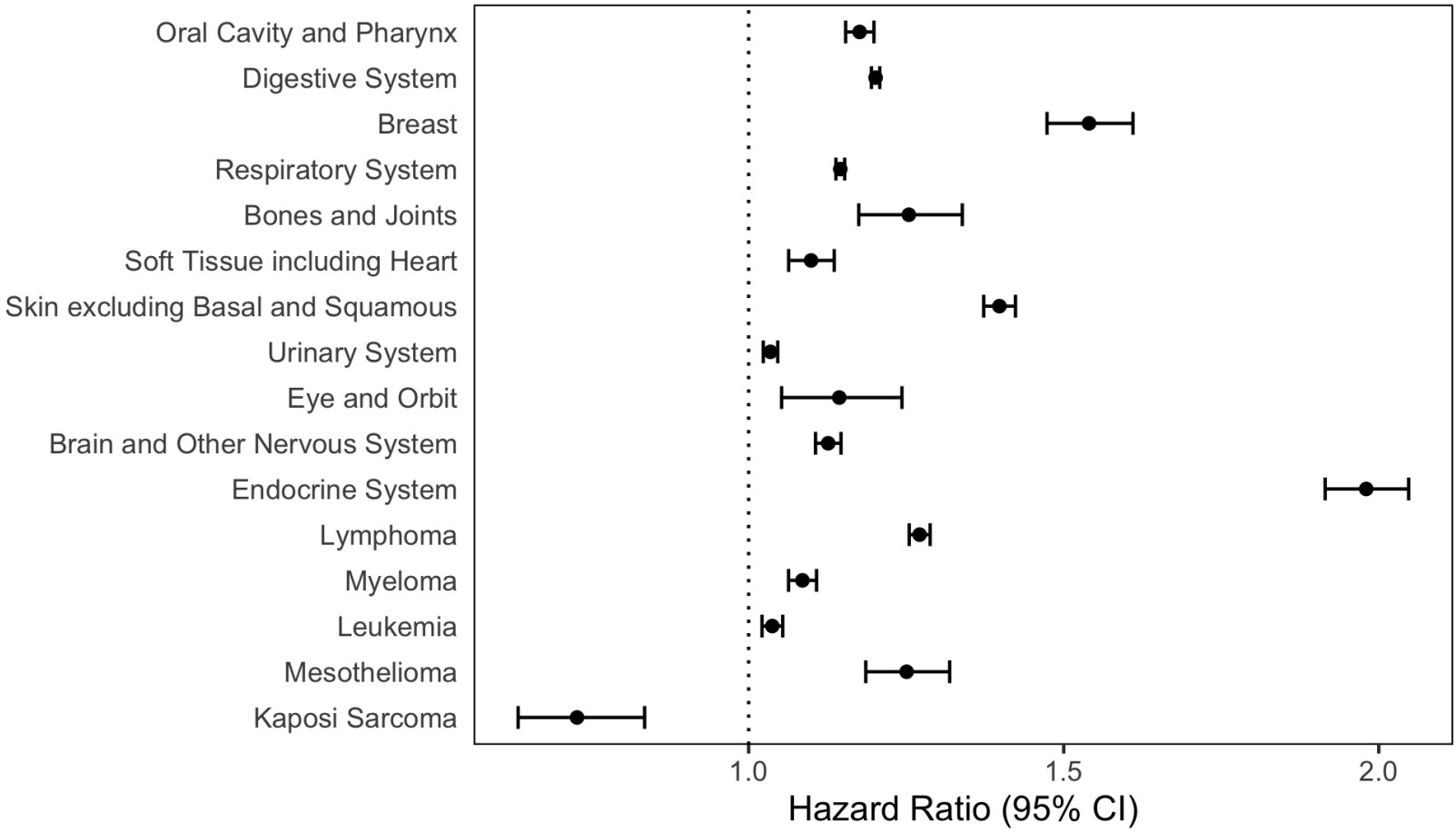

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Figure 4

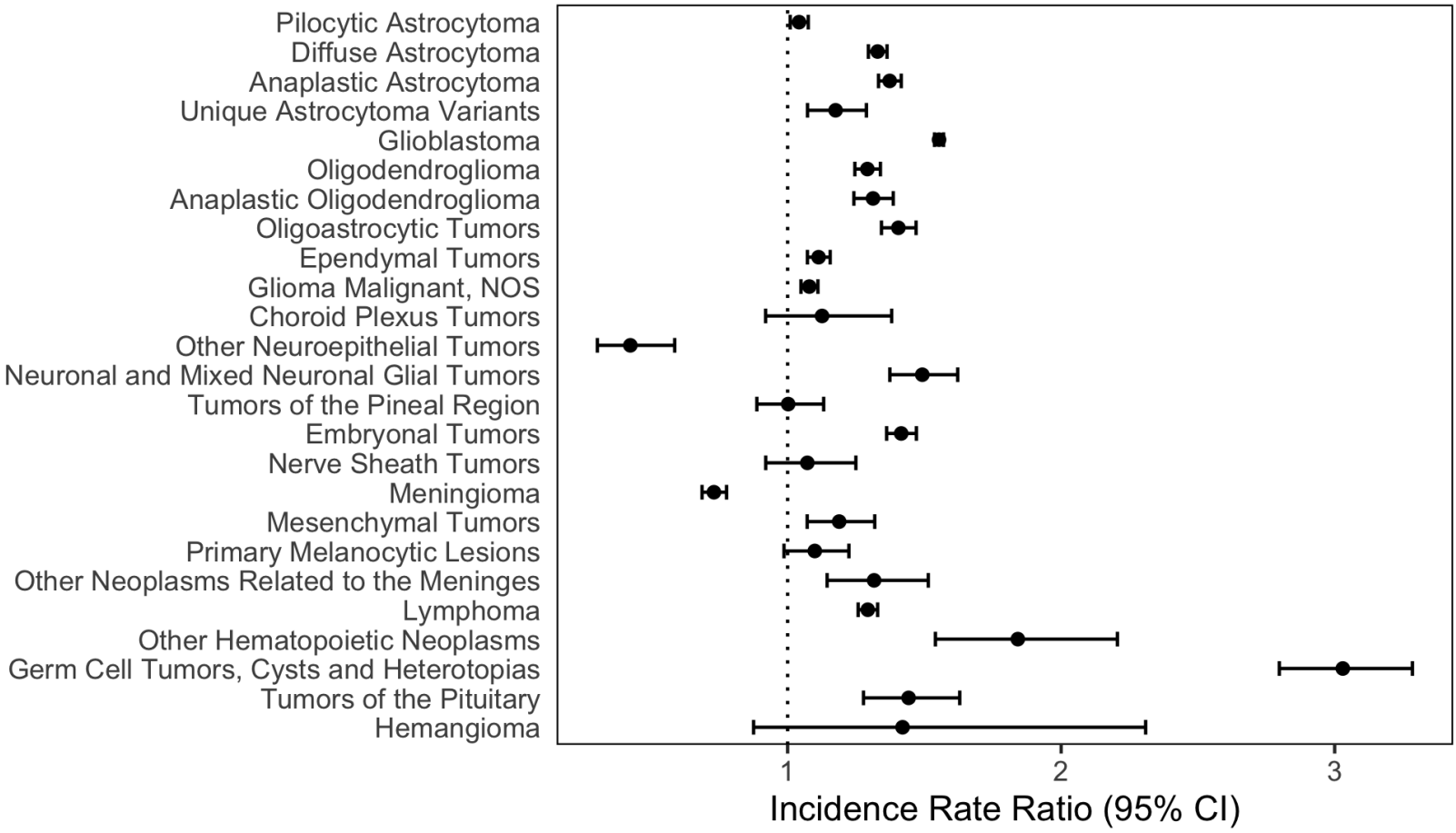

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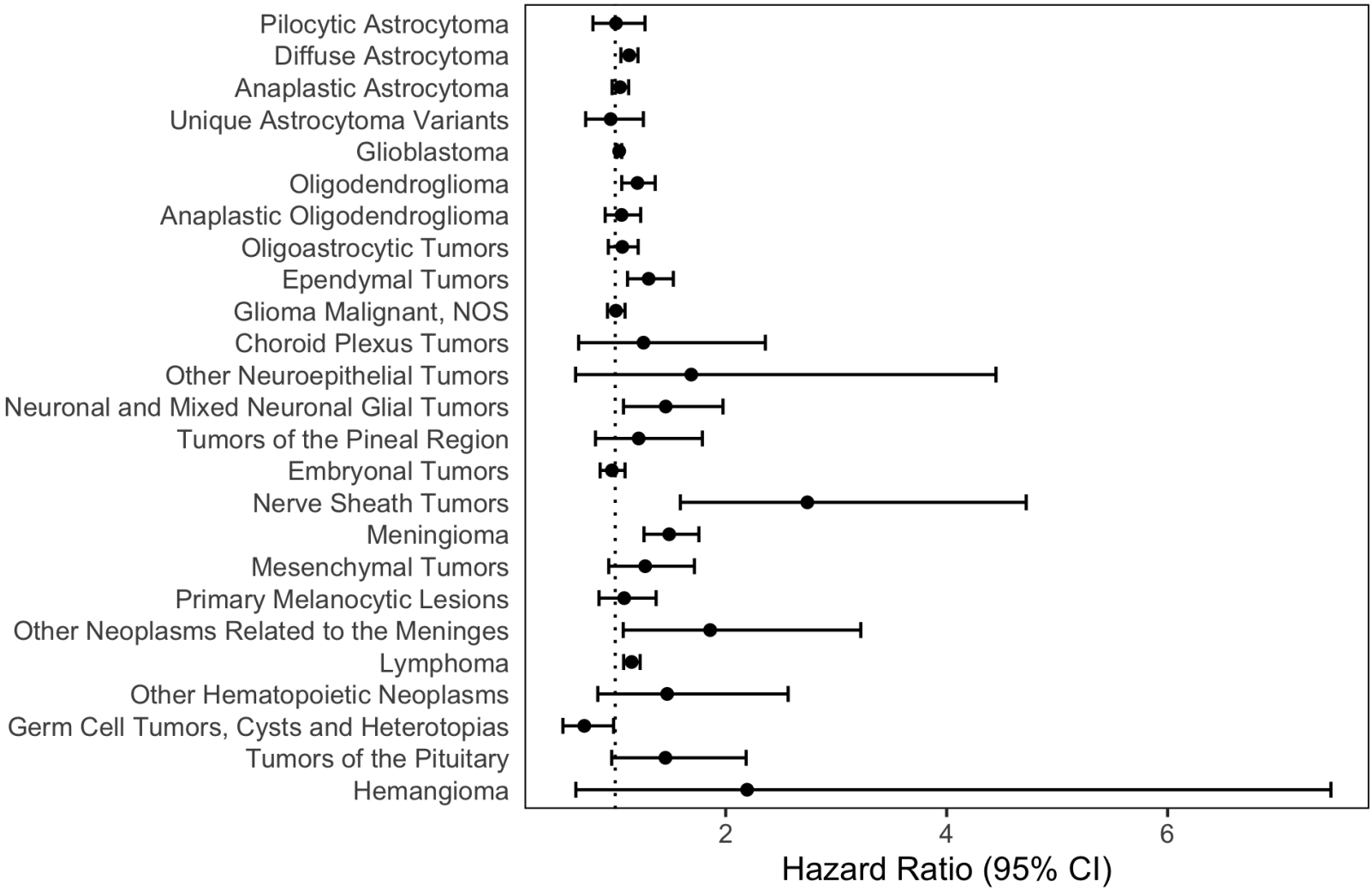
Figure 5



Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

Sex differences in cancer incidence and survival: a pan-cancer analysis

Michelle Dong, Gino Cioffi, Jacqueline Wang, et al.

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