

# Sex Disparities in Cancer Incidence by Period and Age

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## Abstract

**Background:** Cancer epidemiology articles often point out that cancer rates tend to be higher among males than females yet rarely is this theme the subject of investigation.

**Methods:** We used the Surveillance, Epidemiology and End Results program data to compute age-adjusted (2000 U.S. standard population) sex-specific incidence rates and male-to-female incidence rate ratios (IRR) for specific cancer sites and histologies for the period 1975 to 2004.

**Results:** The 10 cancers with the largest male-to-female IRR were Kaposi sarcoma (28.73), lip (7.16), larynx (5.17), mesothelioma (4.88), hypopharynx (4.13), urinary bladder (3.92), esophagus (3.49), tonsil (3.07), oropharynx (3.06), and other urinary organs (2.92). Only 5 cancers had a higher incidence in females compared with males: breast (0.01), peritoneum, omentum, and mesentery (0.18), thyroid (0.39), gall-

bladder (0.57), and anus, anal canal, and anorectum (0.81). Between 1975 and 2004, the largest consistent increases in male-to-female IRR were for cancers of the tonsil, oropharynx, skin excluding basal and squamous, and esophagus, whereas the largest consistent decreases in IRR were for cancers of the lip and lung and bronchus. Male-to-female IRRs varied considerably by age, the largest increases of which were for ages 40 to 59 years for tonsil cancer and hepatocellular carcinoma. The largest decreases in male-to-female IRR by age, meanwhile, were for ages 30 to 49 years for thyroid cancer, ages >70 years for esophageal squamous cell carcinoma, and ages >30 years for lung and bronchus cancer.

**Conclusion:** These observations emphasize the importance of sex in cancer etiopathogenesis and may suggest novel avenues of investigation. (Cancer Epidemiol Biomarkers Prev 2009;18(4):1174–82)

Sex, that is, being male or female, is an important basic human variable that should be considered when designing and analyzing studies in all areas and at all levels of biomedical and health-related research. Differences in health and illness are influenced by individual genetic and physiological constitutions, as well as by an individual's interaction with environmental and experimental factors. The incidence and severity of diseases vary between the sexes and may be related to differences in exposures, routes of entry and the processing of a foreign agent, and cellular responses. (1).

Over the years, many scientific articles have commented that the incidence of a particular cancer is higher in men than women. Other than suggesting that the discrepancies may be due to tobacco and alcohol exposures, relatively little attention has been devoted to exploring the differences in rates. Cancer epidemiology has lacked a strong focus on sex, as many studies have been more

concerned with disease etiology than disease heterogeneity. Even in studies with a focus on heterogeneity, sex is usually little more than a covariate in a statistical model. Despite this, sex is one of the most important variables that need to be considered in the etiology, progression, and treatment of disease (1).

Descriptive epidemiology provides a foundation for many disciplines within medical research. In cancer epidemiology, descriptive analyses of incidence trends often promote the formulation of new ideas and hypotheses. Previous descriptive studies have shown that cancer incidence and mortality rates are much higher in males than females at nearly all ages in the majority of countries (2-10). However, few studies have explicitly set out to focus on sex ratios of cancer incidence, and no study has done this using U.S. data.

This study uses data from the Surveillance, Epidemiology and End Results (SEER) cancer registry program to analyze age-adjusted male-to-female incidence rate ratios (IRR) and sex-specific incidence rates by cancer site, histology, year of diagnosis, and age of diagnosis. It is hoped that this exercise will be hypothesis-generating with regards to sex differences in the etiopathogenesis of cancer.

## Materials and Methods

Data were extracted from the November 2007 submission of the SEER-9 registries database.<sup>1</sup> The variables

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<sup>1</sup> [www.seer.cancer.gov/seerstat](http://www.seer.cancer.gov/seerstat)

calculated were cancer count, person-years, and incidence rate per 100,000 (age-adjusted to the 2000 U.S. standard population) for each cancer, stratified by sex and age (groupings of 1-9, 10-19, ..., 70-79, and  $\geq 80$  years) for the periods 1975 to 1984, 1985 to 1994, 1995 to 2004, and 1975 to 2004. Cancer sites and morphologies investigated were non-sex-specific cancers as defined in the SEER standard site recode groupings.<sup>2</sup> The *International Classification of Diseases for Oncology, Third Edition* codes (11) for the histology-specific analyses were squamous cell carcinoma (SCC; 8050-8078 and 8083-8084), adenocarcinoma (8140-8231, 8250-8551, 8570-8574, and 8576), small cell lung cancer (8002, 8040-8045, 8240, and 8246), large cell lung cancer (8012), hepatocellular carcinoma (HCC; 8170-8175), melanoma (8720-8780), soft-tissue tumors and sarcoma (8680-8711, 8800-8936, 8980-8981, 8990-8991, 9040-9044, 9120-9133, 9150-9252, 9370-9372, 9490, and 9540-9581), transitional cell carcinoma (8120-8139), neuroepithelial tumors (9360-9362, 9381-9421, 9424-9451, 9470-9474, 9490-9501, 9505-9508, and 9522-9523), papillary tumors (8050, 8260, 8340-8344, 8350, and 8450-8460), and anus, anal canal, and anorectal SCC (8050-8078, 8083-8084, and 8124; includes cloacogenic tumors).

Data extraction was restricted to malignant tumors. Male-to-female IRRs were calculated for cancers that had at least 50 cases in each sex by using the male age-adjusted incidence rate as the numerator and the female age-adjusted incidence rate as the denominator. 95% Confidence intervals (95% CI) for the male-to-female IRRs were generated in SEER.<sup>1</sup> Cancers with consistently increasing or decreasing male-to-female IRRs for the period 1975 to 2004 and an incidence rate of at least 0.2 per 100,000 for each sex were tabulated and sorted by relative change in male-to-female IRR. Further investigation was considered for cancers that had the highest incidence in males and/or females, had the highest or lowest male-to-female IRRs, or had the most extreme consistent changes in male-to-female IRR over time. Cancers that qualified for one or more of these groups were not further stratified by histologic group if they had low incidence rates ( $<0.2$  per 100,000) for at least one of the sexes, if further stratification was deemed uninformative, or if the cancer site recode grouping was nonspecific. Selected cancers had their sex-specific incidence rates and male-to-female IRRs tabulated by subsite and/or predominant histologic group(s) for the years 1975 to 1984, 1985 to 1994, 1995 to 2004, and 1975 to 2004.

Graphs were produced for each cancer site/histology, except for cancers that were nonspecific or had low incidence rates in at least one of the sexes. Cancers that had the most extreme consistent changes in male-to-female IRR, an incidence of at least 0.4 per 100,000, and an increasing incidence in at least one of the sexes are illustrated and discussed herein (graphs for other cancers can be accessed online as Supplementary Material). In addition, a graph of total cancer incidence was compiled for the period 1975 to 2004. All graphs show male-to-female IRRs and sex-specific incidence rates plotted by age of diagnosis for age groups 1 to 9, 10

to 19, ..., 70 to 79, and  $\geq 80$  years. Each data point (age group) of these plots was required to have at least 10 cases for each sex. Stata (StataCorp LP, 2007, release 10.1) was used for data processing and analysis. Data were graphed using SigmaPlot (SPSS, 2002, version 11.0).

## Results

Table 1 shows sex-specific, age-adjusted incidence rates and male-to-female IRRs stratified by period for each cancer. During 1975 to 2004, the 10 most common cancers diagnosed among U.S. males were lung and bronchus (93.2 per 100,000 man-years), colon and rectum (70.3), urinary bladder (37.5), non-Hodgkin's lymphoma (21.4), skin excluding basal and squamous (19.7), kidney and renal pelvis (14.8), stomach (14.1), pancreas (13.6), lymphocytic leukemia (8.6), and larynx (8.5). For U.S. females, the 10 most frequent cancers were breast (126.4 per 100,000 woman-years), colon and rectum (51.2), lung and bronchus (45.2), non-Hodgkin's lymphoma (14.4), skin excluding basal and squamous (13.8), pancreas (10.2), urinary bladder (9.6), thyroid (8.9), kidney and renal pelvis (7.2), and stomach (6.4). The 10 cancers with the largest male-to-female IRR during 1975 to 2004 were Kaposi sarcoma (28.73), lip (7.16), larynx (5.17), mesothelioma (4.88), hypopharynx (4.13), urinary bladder (3.92), esophagus (3.49), tonsil (3.07), oropharynx (3.06), and other urinary organs (2.92). During 1975 to 2004, only 5 cancers investigated had a higher incidence in females compared with males: breast (IRR = 0.01), peritoneum, omentum, and mesentery (0.18), thyroid (0.39), gallbladder (0.57), and anus, anal canal and anorectum (0.81).

Table 2 shows the relative change in male-to-female IRRs and relative change in sex-specific incidence rates for the periods 1985 to 1994 and 1995 to 2004 compared with 1975 to 1984 for cancers showing a consistently increasing or decreasing IRR and incidence rates for each sex of at least 0.2 per 100,000 listed according to percent change in IRR. During 1975 to 2004, tonsil cancer had the largest increase in male-to-female IRR, and this was the result of an increasing male incidence and decreasing female incidence. Other cancers with increasing IRRs were esophagus and mesothelioma, the former due to increases among males not apparent among females and the latter a female decrease in incidence. Rates for the remaining cancers with increasing male-to-female IRRs increased among both sexes but more so among males than females.

Many cancers had a decline in the male-to-female IRR during 1975 to 2004. The IRRs for the cancer sites ureter, floor of mouth, retroperitoneum, and lip decreased due to faster declines in male incidence than in female incidence. Reductions in IRR for other cancers (pancreas, nose, nasal cavity and middle ear, gum and other mouth, Hodgkin's lymphoma, and larynx) were solely caused by decreased male incidence, with female rates remaining fairly stable. More rapidly increasing rates among females than males reduced the IRRs for cancers of the kidney and renal pelvis, cranial nerves and other nervous system, and thyroid. Perhaps the most notable declining IRR was that for lung and bronchus cancer, which is singular in that it was caused by a simultaneous decrease in male rates and increase in female rates.

<sup>2</sup> [http://seer.cancer.gov/siterecode/icdo3\\_d01272003/](http://seer.cancer.gov/siterecode/icdo3_d01272003/)

**Table 1. Incidence rates and male-to-female IRRs by cancer, 1975 to 2004**

Site	Cancer incidence per 100,000 man/woman-years								Male-to-female IRR (95% CI)			
	1975-1984		1985-1994		1995-2004		1975-2004		1975-1984	1985-1994	1995-2004	1975-2004
	Male	Female	Male	Female	Male	Female	Male	Female				
Lip	4.51	0.43	3.00	0.42	1.93	0.40	2.98	0.42	10.54	7.18	4.77	7.16 (6.77-7.57)
Tongue	3.58	1.55	3.71	1.63	3.98	1.64	3.79	1.62	2.31	2.28	2.42	2.34 (2.27-2.42)
Salivary gland	1.38	0.96	1.57	0.92	1.62	1.03	1.54	0.97	1.44	1.71	1.57	1.59 (1.51-1.66)
Floor of mouth	2.36	0.87	1.88	0.70	1.24	0.51	1.76	0.68	2.71	2.69	2.43	2.59 (2.47-2.73)
Gum and other mouth	2.95	1.72	2.62	1.73	2.07	1.47	2.49	1.63	1.72	1.51	1.41	1.53 (1.47-1.58)
Nasopharynx	1.07	0.42	1.05	0.41	1.02	0.43	1.04	0.42	2.53	2.58	2.36	2.48 (2.33-2.64)
Tonsil	1.88	0.77	1.92	0.69	2.22	0.55	2.04	0.66	2.43	2.79	4.01	3.07 (2.92-3.22)
Oropharynx	1.53	0.20	0.53	0.17	0.50	0.15	0.52	0.17	2.69	3.12	3.37	3.06 (2.79-3.37)
Hypopharynx	2.19	0.56	2.11	0.48	1.43	0.35	1.87	0.45	3.89	4.37	4.14	4.13 (3.9-4.37)
Other oral cavity and pharynx	0.69	0.24	0.68	0.26	0.45	0.16	0.59	0.22	2.86	2.58	2.76	2.7 (2.48-2.94)
Esophagus	6.98	2.22	7.73	2.25	8.20	2.15	7.72	2.21	3.14	3.43	3.82	3.49 (3.4-3.59)
Stomach	16.84	7.75	14.59	6.43	11.92	5.56	14.10	6.43	2.17	2.27	2.15	2.19 (2.16-2.23)
Small intestine	1.35	0.97	1.86	1.24	2.22	1.59	1.86	1.30	1.39	1.50	1.39	1.43 (1.38-1.49)
Colon and rectum	75.07	56.02	74.46	52.13	63.99	46.92	70.33	51.16	1.34	1.43	1.36	1.37 (1.37-1.38)
Anus, anal canal, and anorectum	0.79	1.04	0.95	1.21	1.24	1.47	1.02	1.27	0.76	0.78	0.85	0.81 (0.77-0.85)
Liver and intrahepatic bile duct	4.27	1.70	5.98	2.24	8.68	3.20	6.60	2.46	2.51	2.67	2.71	2.69 (2.62-2.76)
Gallbladder	1.23	2.21	0.96	1.77	0.88	1.41	1.00	1.74	0.56	0.54	0.63	0.57 (0.55-0.6)
Other biliary	1.97	1.33	1.81	1.23	1.99	1.28	1.93	1.27	1.48	1.47	1.56	1.52 (1.46-1.58)
Pancreas	14.53	10.04	13.48	10.27	13.19	10.25	13.65	10.20	1.45	1.31	1.29	1.34 (1.32-1.36)
Retroperitoneum	0.55	0.43	0.49	0.42	0.44	0.41	0.49	0.42	1.28	1.17	1.08	1.17 (1.09-1.26)
Peritoneum, omentum, and mesentery	0.06	0.07	0.10	0.27	0.09	0.95	0.09	0.47	0.85	0.36	0.10	0.18 (0.16-0.21)
Other digestive organs	0.47	0.36	0.44	0.31	0.55	0.46	0.49	0.38	1.29	1.41	1.19	1.28 (1.18-1.38)
Nose, nasal cavity, and middle ear	1.01	0.52	0.98	0.60	0.86	0.54	0.94	0.56	1.93	1.62	1.61	1.7 (1.6-1.8)
Larynx	9.97	1.66	9.15	1.83	6.96	1.51	8.53	1.65	6.00	5.00	4.62	5.17 (5.02-5.32)
Lung and bronchus	98.89	32.97	98.49	47.36	84.28	52.47	93.16	45.18	3.00	2.08	1.61	2.06 (2.05-2.07)
Trachea, mediastinum, and other respiratory organs	0.43	0.16	0.36	0.16	0.28	0.12	0.35	0.15	2.64	2.19	2.44	2.4 (2.15-2.67)
Bones and joints	1.01	0.73	1.04	0.75	1.03	0.79	1.03	0.76	1.39	1.40	1.30	1.35 (1.28-1.42)
Soft-tissue including heart	2.75	1.91	2.96	2.10	3.60	2.46	3.15	2.18	1.44	1.41	1.46	1.45 (1.4-1.49)
Skin excluding basal and squamous	12.07	10.06	18.87	13.26	25.51	16.97	19.70	13.81	1.20	1.42	1.50	1.43 (1.41-1.44)
Breast	0.97	107.00	1.09	131.98	1.19	136.11	1.10	126.38	0.01	0.01	0.01	0.01 (0.01-0.01)
Urinary bladder	36.13	9.37	38.15	9.64	37.94	9.71	37.54	9.57	3.85	3.96	3.91	3.92 (3.87-3.97)
Kidney and renal pelvis	12.04	5.41	14.69	7.13	16.94	8.52	14.84	7.17	2.22	2.06	1.99	2.07 (2.04-2.1)
Ureter	1.10	0.43	0.95	0.38	0.85	0.37	0.96	0.39	2.54	2.52	2.30	2.45 (2.29-2.61)
Other urinary organs	0.67	0.24	0.56	0.21	0.54	0.16	0.58	0.20	2.77	2.70	3.34	2.92 (2.67-3.2)
Eye and orbit	1.01	0.76	0.95	0.64	0.95	0.67	0.97	0.69	1.33	1.48	1.42	1.41 (1.33-1.49)
Brain	7.13	4.80	7.88	5.38	7.57	5.18	7.55	5.15	1.48	1.46	1.46	1.47 (1.44-1.5)
Cranial nerves, other nervous system	0.38	0.30	0.43	0.37	0.43	0.40	0.42	0.36	1.25	1.18	1.07	1.16 (1.07-1.25)
Thyroid	2.90	6.61	3.19	7.75	4.18	11.62	3.50	8.93	0.44	0.41	0.36	0.39 (0.38-0.4)
Other endocrine including thymus	0.58	0.40	0.66	0.52	0.75	0.58	0.67	0.51	1.47	1.28	1.28	1.32 (1.24-1.41)
Hodgkin's lymphoma	3.64	2.38	3.47	2.58	3.15	2.54	3.40	2.51	1.53	1.35	1.24	1.35 (1.32-1.39)
Non-Hodgkin's lymphoma	15.14	11.18	22.39	14.50	24.64	16.61	21.35	14.40	1.35	1.54	1.48	1.48 (1.47-1.5)
Myeloma	6.38	4.28	7.07	4.75	7.33	4.78	6.98	4.64	1.49	1.49	1.53	1.51 (1.47-1.54)
Lymphocytic leukemia	8.41	4.49	8.80	4.61	8.56	4.57	8.56	4.55	1.88	1.91	1.87	1.88 (1.84-1.92)
Myeloid and monocytic leukemia	7.70	4.73	7.07	4.55	7.47	4.77	7.38	4.67	1.63	1.56	1.57	1.58 (1.55-1.61)
Other leukemia	1.36	0.77	1.62	0.92	1.13	0.72	1.36	0.80	1.78	1.76	1.56	1.69 (1.61-1.78)
Mesothelioma	1.50	0.34	2.05	0.41	2.04	0.41	1.91	0.39	4.42	4.98	5.03	4.88 (4.59-5.18)
Kaposi sarcoma	1.10	0.12	8.14	0.16	2.27	0.13	3.96	0.14	9.29	50.52	17.57	28.73 (26.27-31.47)

NOTE: SEER\*Stat Database: Incidence-SEER-9 Registries Limited-Use, November 2007 Submission (1973-2005). Rates are per 100,000 and age-adjusted to the 2000 U.S. standard population (19-age groups; Census P25-1130).

Of the cancer sites in Table 2, those with the largest increases in male incidence between periods 1975 to 1984 and 1995 to 2004 were skin excluding basal and squamous (111%), liver and intrahepatic bile duct

(103%), anus, anal canal, and anorectum (58%), and thyroid (44%). For females, the cancer sites were liver and intrahepatic bile duct (88%), thyroid (76%), skin excluding basal and squamous (69%), and lung and

**Table 2. Male-to-female IRRs and percent changes for selected cancers, 1975 to 2004**

Site	Male-to-female IRR			% Change in male-to-female IRR		% Change in male incidence rate		% Change in female incidence rate	
	1975-1984	1985-1994	1995-2004	1985-1994 vs 1975-1984	1995-2004 vs 1975-1984	1985-1994 vs 1975-1984	1995-2004 vs 1975-1984	1985-1994 vs 1975-1984	1995-2004 vs 1975-1984
Tonsil	2.43	2.79	4.01	15	65	2	18	-11	-29
Skin excluding basal and squamous	1.20	1.42	1.50	19	25	56	111	32	69
Esophagus	3.14	3.43	3.82	9	21	11	17	1	-3
Mesothelioma	4.42	4.98	5.03	13	14	36	36	21	20
Anus, anal canal, and anorectum	0.76	0.78	0.85	3	12	20	58	17	41
Liver and intrahepatic bile duct	2.51	2.67	2.71	6	8	40	103	32	88
Brain	1.48	1.46	1.46	-1	-2	10	6	12	8
Ureter	2.54	2.52	2.30	-1	-9	-13	-23	-13	-15
Floor of mouth	2.71	2.69	2.43	-1	-11	-21	-48	-20	-41
Kidney and renal pelvis	2.22	2.06	1.99	-7	-11	22	41	32	57
Pancreas	1.45	1.31	1.29	-9	-11	-7	-9	2	2
Other leukemia	1.78	1.76	1.56	-1	-12	19	-17	20	-6
Cranial nerves, other nervous system	1.25	1.18	1.07	-6	-14	16	14	23	33
Retropertoneum	1.28	1.17	1.08	-9	-15	-11	-19	-2	-4
Nose, nasal cavity, and middle ear	1.93	1.62	1.61	-16	-17	-3	-15	15	3
Gum and other mouth	1.72	1.51	1.41	-12	-18	-11	-30	1	-14
Thyroid	0.44	0.41	0.36	-6	-18	10	44	17	76
Hodgkin's lymphoma	1.53	1.35	1.24	-12	-19	-5	-14	8	7
Larynx	6.00	5.00	4.62	-17	-23	-8	-30	10	-9
Lung and bronchus	3.00	2.08	1.61	-31	-46	0	-15	44	59
Lip	10.54	7.18	4.77	-32	-55	-33	-57	-2	-5

NOTE: SEER\*Stat Database: Incidence-SEER-9 Registries Limited-Use, November 2007 Submission (1973-2005). Rates are per 100,000 and age-adjusted to the 2000 U.S. standard population (19-age groups; Census P25-1130).

bronchus (59%). Over the same period, the sites with the largest decreases in incidence have been lip (57%), floor of mouth (48%), larynx (30%), and gum and other mouth (30%) for males and floor of mouth (41%), tonsil (29%), ureter (15%), and gum and other mouth (14%) for females.

Table 3 shows sex-specific incidence rates and male-to-female IRRs for specific histologic groups of selected cancers. The rates and IRRs for nearly all histologic groups follow the same trends as their parent cancer site. However, this is not true for the two histologic types of esophageal cancer, which trended in opposite directions. The IRR, by 10-year period, for all esophageal cancers combined increased from 3.14 to 3.43 to 3.82 (Table 1); however, this is a combination of increasing IRRs for esophageal adenocarcinoma (6.25, 7.96, and 7.69) and decreasing IRRs for esophageal SCC (2.93, 2.57, and 2.25; Table 3). Although the IRRs did not change greatly over time, the IRRs for HCC ranged 3.44 to 3.56, considerably larger than those for intrahepatic bile duct carcinoma which ranged from 1.51 to 1.62, not apparent in the overall IRR for liver and intrahepatic bile duct cancer range of 2.51 to 2.71. In contrast to the overall lung and bronchus cancer IRR of 2.06, which declined from 3.00 to 1.61 over the decades, the overall IRR ranged from 3.50 for SCC to 2.19 for large cell, 1.60 for small cell, and 1.53 for adenocarcinoma; IRRs for each type declined from an early maximum of 5.29 for squamous cell to 1.26 for small cell carcinoma recently.

Incidence rates and male-to-female IRRs are plotted by age of diagnosis for nine cancer sites/histologies

(Fig. 1A-I) selected because they had the most extreme consistent changes in male-to-female IRR and an incidence of at least 0.4 per 100,000, which was increasing in at least one of the sexes (graphs for other cancers, Supplementary Figs. S1-30, can be accessed online). During the earliest decade, the male-to-female IRR for tonsil cancer was ~2 at ages <70 years and increased to ~4 at older ages; by the recent decade, increasing male rates and declining female rates resulted in a male-to-female IRR of >5 at ages 40 to 59 years (Fig. 1A). Rates for the cancer site skin excluding basal and squamous (Fig. 1B) predominated among females at younger ages (<40 years) and among males in the older age groups (≥40 years), and rates increased over time more rapidly among younger women and among older men, resulting in declines in the male-to-female IRR at younger ages and increases at older ages. The incidence of esophageal SCC among males at all ages and in females ages <70 years declined, and the male-to-female IRR decreased at older ages from ~3 to 2 (Fig. 1C). The male-to-female IRR for esophageal adenocarcinoma exceeded 10 at ages 50 to 59 years and declined with age to 4 to 5 at the oldest ages (Fig. 1D). Rates for anus, anal canal, and anorectal cancers increased comparably in both sexes in nearly all age groups, making the male-to-female IRR fairly stable and <1 at ages >50 years (Fig. 1E). The increasing rates of HCC in younger age groups (<50 years) has been more rapid among males than females, and the male-to-female IRR increased from <3 to >5, in contrast to decreases in the male-to-female



IRR at older ages (Fig. 1F). Kidney and renal pelvis cancer IRR were  $\sim 1$  at very young ages (Wilms' tumors), decreased over the decades at ages 10 to 39 years, and increased to a fairly constant two at older ages in spite of increasing rates (Fig. 1G). Thyroid cancer male-to-female IRR were  $\sim 0.2$  at ages 20 to 29 years and increased to at least 0.7 at the oldest ages; rates increased over time more rapidly among younger women and older men, leading to progressively lower IRRs (Fig. 1H). Male rates for lung and

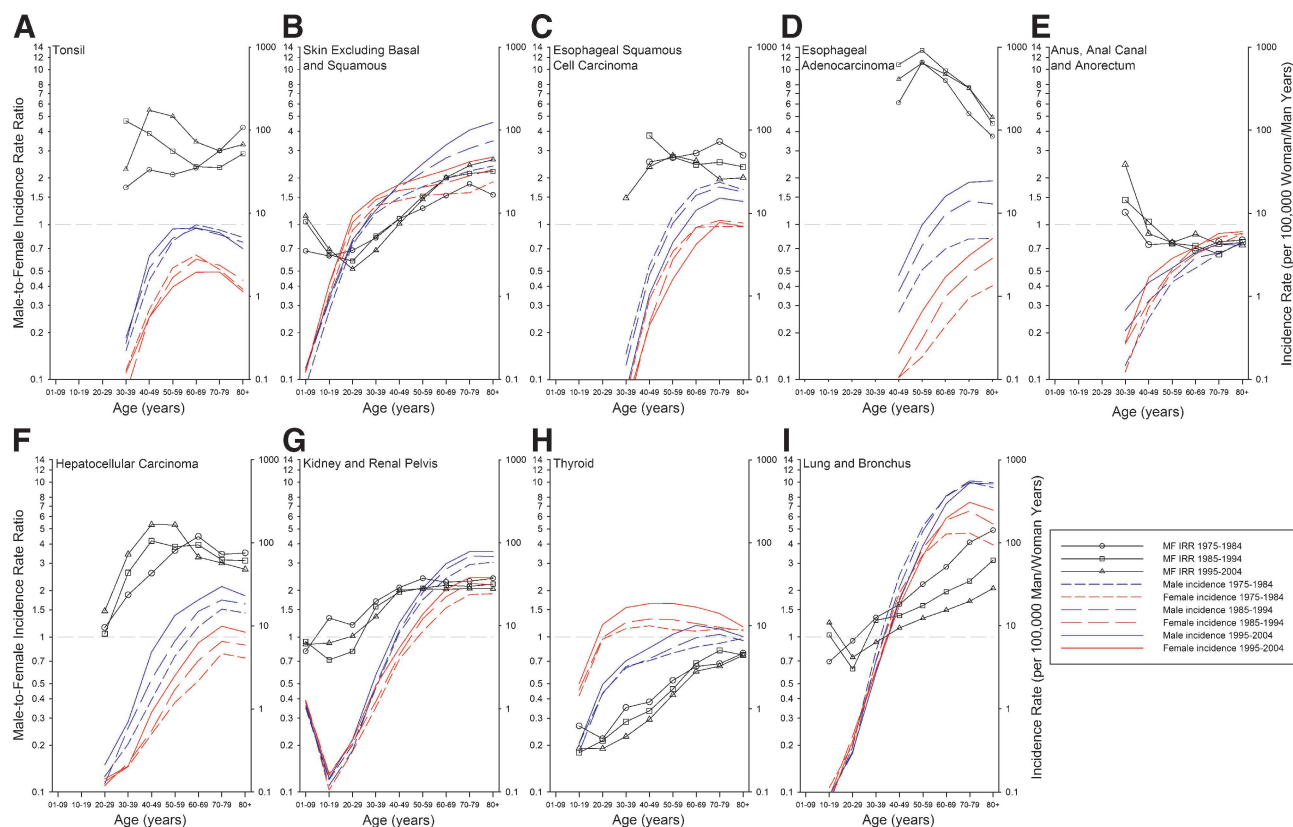
bronchus malignancies declined slightly at virtually all ages, whereas female rates increased, especially in the age groups of  $\geq 60$  years (Fig. 1I), and the male-to-female IRR declined dramatically across all adult age groups, dropping below 1 in recent years among those ages  $< 40$  years.

Rates during the period 1975 to 2004 for all cancers combined and for all cancers excluding the sex-specific sites were higher among females than males at adult ages  $< 50$  years and clearly higher among males than females

**Table 3. Incidence rates and male-to-female IRRs by cancer site and histology, 1975 to 2004**

Site	Cancer incidence per 100,000 man/woman-years								Male-to-female IRR			
	1975-1984		1985-1994		1995-2004		1975-2004		1975-1984	1985-1994	1995-2004	1975-2004
	Male	Female	Male	Female	Male	Female	Male	Female				
Lip												
SCC	4.39	0.38	2.93	0.37	1.85	0.36	2.89	0.37	11.68	7.95	5.19	7.88
Tonsil												
SCC	1.75	0.72	1.84	0.66	2.12	0.53	1.94	0.63	2.43	2.80	4.01	3.08
Hypopharynx												
SCC	2.08	0.52	2.01	0.46	1.37	0.33	1.78	0.43	3.98	4.35	4.17	4.16
Esophagus												
SCC	4.93	1.68	4.21	1.64	2.86	1.27	3.88	1.51	2.93	2.57	2.25	2.57
Adenocarcinoma	1.09	0.17	2.66	0.33	4.57	0.59	2.99	0.39	6.25	7.96	7.69	7.64
Stomach												
Adenocarcinoma	14.27	6.16	12.98	5.44	10.39	4.53	12.29	5.28	2.32	2.39	2.30	2.33
Colon												
Adenocarcinoma	46.98	37.22	49.31	36.59	42.30	33.19	45.83	35.46	1.26	1.35	1.27	1.29
Rectum and rectosigmoid junction												
Adenocarcinoma	22.37	13.60	20.80	11.87	17.60	10.18	19.94	11.70	1.64	1.75	1.73	1.70
Anus, anal canal, and anorectum												
SCC	0.47	0.76	0.57	0.91	0.89	1.14	0.68	0.97	0.62	0.63	0.78	0.70
Liver and Intrahepatic bile duct												
HCC	2.92	0.85	4.15	1.20	6.48	1.82	4.75	1.34	3.44	3.46	3.56	3.55
Intrahepatic bile duct	0.22	0.15	0.75	0.46	0.94	0.62	0.69	0.44	1.53	1.62	1.51	1.56
Gallbladder												
Adenocarcinoma	1.02	1.87	0.78	1.51	0.71	1.17	0.81	1.47	0.55	0.52	0.61	0.56
Pancreas												
Adenocarcinoma	8.87	6.20	8.80	6.62	8.99	6.86	8.91	6.59	1.43	1.33	1.31	1.35
Larynx												
SCC	9.49	1.57	8.77	1.74	6.67	1.43	8.17	1.57	6.06	5.04	4.65	5.21
Lung and bronchus												
SCC	32.51	6.15	28.34	8.20	19.31	7.74	26.02	7.44	5.29	3.46	2.50	3.50
Adenocarcinoma	21.27	11.15	26.12	16.71	24.60	18.73	24.21	15.84	1.91	1.56	1.31	1.53
Small cell	14.12	6.10	14.87	9.36	11.57	9.19	13.39	8.35	2.31	1.59	1.26	1.60
Large cell	6.39	2.21	7.99	3.73	4.05	2.30	6.00	2.74	2.89	2.14	1.76	2.19
Skin excluding basal and squamous												
Melanoma	11.12	9.34	17.16	12.13	23.20	15.52	17.94	12.67	1.19	1.42	1.49	1.42
Breast												
Adenocarcinoma	0.89	99.24	1.01	125.79	1.12	131.41	1.02	120.3	0.01	0.01	0.01	0.01
Retroperitoneum												
Soft-tissue and sarcoma	0.41	0.36	0.39	0.36	0.36	0.34	0.39	0.35	1.14	1.09	1.06	1.09
Kidney and renal pelvis												
Adenocarcinoma	9.10	3.94	12.05	5.69	14.48	7.09	12.18	5.72	2.31	2.12	2.04	2.13
Urinary bladder												
Transitional cell carcinoma	32.51	8.05	35.79	8.66	35.77	8.92	34.91	8.57	4.04	4.13	4.01	4.07
Ureter												
Transitional cell carcinoma	1.01	0.39	0.88	0.35	0.81	0.34	0.89	0.36	2.59	2.54	2.39	2.50
Thyroid												
Papillary	1.95	4.79	2.25	6.12	3.28	9.94	2.58	7.23	0.41	0.37	0.33	0.36

NOTE: SEER\*Stat Database: Incidence-SEER-9 Registries Limited-Use, November 2007 Submission (1973-2005). Rates are per 100,000 and age-adjusted to the 2000 U.S. standard population (19-age groups; Census P25-1130).



**Figure 1.** Male-to-female IRRs and sex-specific incidence rates by age, 1975 to 2004. **A.** Tonsil. **B.** Skin excluding basal and squamous. **C.** Esophageal squamous cell carcinoma. **D.** Esophageal adenocarcinoma. **E.** Anus, anal canal, and anorectum. **F.** Hepatocellular carcinoma. **G.** Kidney and renal pelvis. **H.** Thyroid. **J.** Lung and bronchus. *MF IRR*, male-to-female IRR.

at ages  $\geq 60$  years (Fig. 2). When rates for total cancer excluding the sex-specific sites and breast cancer are considered, the male-to-female IRR exceeds 1 at all ages  $\geq 30$  years. Across all ages combined, the cancer burden was higher in males than females for total cancer (male-to-female IRR, 1.37; 95% CI, 1.37-1.38), total cancer excluding sex-specific sites (1.14; 95% CI, 1.14-1.14), and total cancer excluding sex-specific sites and breast cancer (1.77; 95% CI, 1.76-1.77).

## Discussion

Sex disparities in cancer incidence have often been acknowledged but have rarely been the focus of interest in the epidemiologic literature. This is despite the fact that this variable accounts for considerable differences in carcinogenic exposure and biology. As seen in the results of this study, ratios of incidence by sex and changes in those ratios may be helpful in generating new hypotheses or in substantiating old hypotheses.

Tonsil and oropharyngeal cancers increased in male predominance between 1975 and 2004. These two cancer sites have the strongest and most consistent associations with human papillomavirus (HPV)-16 infection of all the oral cancer sites (12). Although tobacco and alcohol are known to be important risk factors for head and neck

malignancies (13, 14), historical trends indicate that these exposures are not diverging between the sexes (15).<sup>3,4</sup> This suggests that other risk factors, including oral HPV infection, could be driving the increases in male-to-female IRRs of these sites. Evidence to support this is that increased and earlier sexual activity in males, but perhaps not in females, increases the risk of HPV-16-associated oral cancer (16). In addition, two studies have shown increased risks of oral HPV-16/HPV-18/HPV-33 (17) and head and neck cancer (18) in male partners of females diagnosed with various cervical abnormalities. In total, this evidence may support a speculative hypothesis of differential transmission risks between males and females when engaging in opposite sex, genital-oral sexual practices (17, 19).

At younger ages, skin excluding basal and squamous (Fig. 1B) exhibited a slow but progressive increased female incidence compared with the relatively stable rates of males. Intermittent exposure to high doses of ultraviolet radiation is the main risk factor for this tumor site (20), and the suggestion that females attempt to tan

<sup>3</sup> <http://www.niaaa.nih.gov/Resources/DatabaseResources/QuickFacts/AlcoholConsumption/PercentAlcoholGender.htm>

<sup>4</sup> <http://www.niaaa.nih.gov/Resources/DatabaseResources/QuickFacts/AlcoholConsumption/dkpat18.htm>

more than males may explain the increased incidence of melanoma in younger females (21). Alternative explanatory factors include hypotheses of a hormonal etiology (22) and an association with increasing body mass index/body surface area (23). In contrast to the female predominance at younger ages, male incidence rates predominated and increased at a greater pace beyond age 40 years, which caused the IRR to inflate. One possible explanation may be the greater lifetime sun exposure in men with outdoor occupations.

The two predominant histologic types of esophageal cancer (Table 3; Fig. 1C and D) have diverged in both their incidence and male-to-female IRRs. The IRR for esophageal adenocarcinoma increased then stabilized, a pattern unlikely to be accounted for by alcohol and tobacco due to their historical trends and stronger

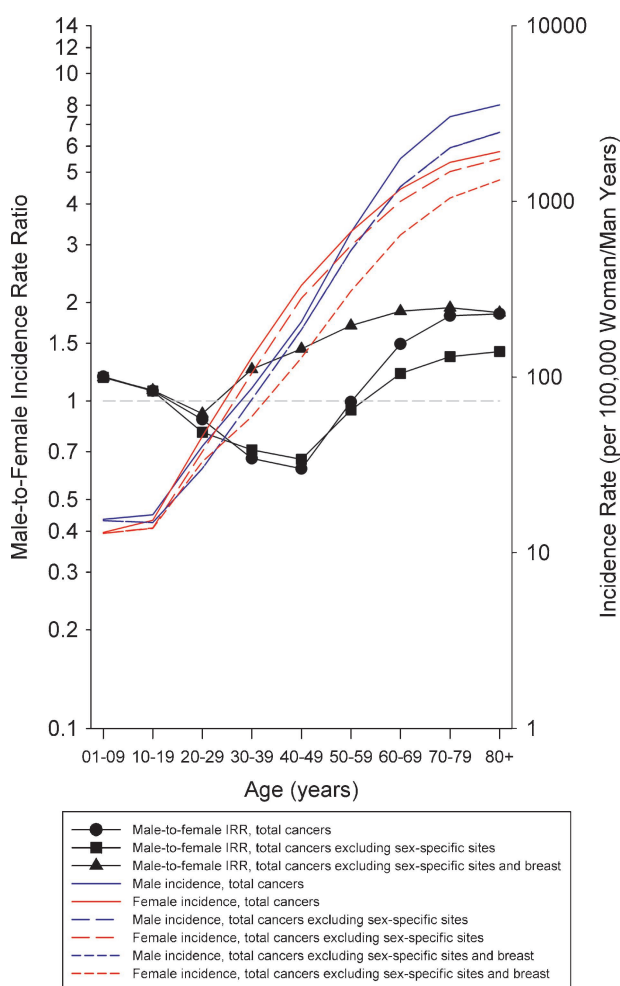
associations with esophageal SCC relative to esophageal adenocarcinoma (24). Preneoplastic states following severe reflux exhibit an increasing male predominance in the stepwise progression to adenocarcinoma (25), which may indicate that the causal exposure(s) of the sex disparity is important at all stages of disease. There is some evidence to suggest that erosive reflux disease may be more prevalent in males at earlier ages compared with females (26, 27). Other risk factors, including estrogen exposure (28, 29), body mass index (30), and *Helicobacter pylori* infection (31),<sup>5</sup> have provided no evidence for being the causal agents of the sex ratio imbalance. Putative differences between the sexes that may explain the male predominance of esophageal adenocarcinoma include android obesity (32), production and concentration of gastric acid (33), hiatal hernia (34), defective lower esophageal sphincter (34), and higher intra-abdominal and intragastric pressures (35).

Cancers of the anus, anal canal, and anorectum is one of just a few cancers that were more common in females than males at nearly all ages (Fig. 1E). Cloacogenic tumors, a subtype of SCC that contributes 15% of the malignancies of this site, are more common in females (IRR, 0.49; 1975-2004), but this does not fully account for the female predominance of these tumors (IRR, 0.77; 1975-2004, for SCC excluding cloacogenic tumors). A potential reason for the increasing predominance of females may be evolving sexual practices given the putative association of these cancers with anal HPV infections (36, 37).

HCC rates increased among both sexes at older ages, but especially among males ages <60 years (Fig. 1F). Major risk factors for HCC in the United States are chronic infection with hepatitis C and B virus as well as alcoholic liver disease (38). Chronic hepatitis B and C infections are more common in males than in females (39) and this difference is likely to account for some of the disparity in IRRs. Historical trends of alcohol consumption<sup>5,6</sup> imply this to be an unlikely cause of the diverging male-to-female IRRs at younger ages. The strongest hypothesis to date, which may account for the sex disparity in incidence, is the anticarcinogenic effect of estrogen, which constrains transcription of the proinflammatory cytokine interleukin-6 gene, leading to a decrease in HCC (40). Increased body mass index (41) and diabetes (42) have also been associated with increased risk of HCC, although it is not clear that either exposure could account for the increased male-to-female IRR at younger ages (43).<sup>6</sup>

The male-to-female IRR for kidney and renal pelvis cancer has not significantly changed (Table 1). Moreover, although the incidence in males and females has been increasing, the IRR for adult malignancies has remained stable at ~2 (Fig. 1G). Therefore, it is unlikely that associated exposures of tobacco (44, 45) and obesity (45) are major factors in the male predominance of this cancer site, as these exposures have been changing over time. Reasons for the sex discrepancy of cancer incidence at this site remain unresolved.

Between 1975 and 2004, thyroid cancer incidence was higher in females than males at all ages (Fig. 1H). The



**Figure 2.** Male-to-female IRRs and sex-specific incidence rates by age for total cancer, total cancer excluding sex-specific sites, and total cancer excluding sex-specific sites and breast, 1975 to 2004. Note that the lines for “Male incidence, total cancer excluding sex-specific sites” and “Male incidence, total cancer excluding sex-specific sites and breast” are virtually identical due to the low incidence of breast cancer in males relative to male total cancer incidence.

<sup>5</sup> L.A. Anderson, 2008, personal communication.

<sup>6</sup> <http://www.cdc.gov/diabetes/statistics/prev/national/fig2004.htm>

etiology of this cancer is poorly understood (46), but increased female incidence during reproductive ages suggests a possible hormonal pathogenesis (47). Evidence from autopsy studies indicates that the prevalence of thyroid microcarcinoma is equivalent between the sexes, whereas females account for ~83% of clinical cases (48). This may indicate that females have an increased propensity for diagnostic investigation given their higher rates of thyroid disease relative to males.

The male-to-female IRRs for lung and bronchus cancer reflect historical exposure to tobacco smoking; as smoking habits have converged between the sexes (15), so has the incidence (Fig. 1I). This pattern is also evident for other cancers for which tobacco smoking is a risk factor, including lip (Supplementary Fig. S1), and, at older ages, esophageal SCC (Fig. 1C), floor of mouth (Supplementary Fig. S4), and larynx (Supplementary Fig. S16). The dramatic decrease in the IRR in later periods for cancers of the lung and bronchus exemplifies the effect that a single sex-discrepant exposure can have on cancer incidence.

The vast majority of cancers included in this review have higher incidence rates in males than in females, as accentuated in Fig. 2, and this suggests the possibility of universal mechanisms that increase male susceptibility to cancer. Tentative explanatory hypotheses include sex differences in antioxidative capacity (49), metal toxicity (50), beliefs and behaviors (51), health-care access and utilization (43), sex chromosome complement/aneuploidy/aberrations (52), gene expression (53), hormones (54), immunocompetence (55), and the disposable soma theory of aging (56).

The main strength of male-to-female IRRs, relative to absolute differences in incidence rates, is that they are less likely to be affected by changes in diagnostic techniques, preventative strategies, tumor definitions, and coding practices (57); changes in such parameters may not be expected to affect the sexes disproportionately. Male-to-female IRRs, however, are still subject to the effects of sex differences in reporting behavior, illness behavior, health-care access and utilization, and physician behavior (9, 58). In spite of these unavoidable caveats, the use of a sex ratio statistic is still advantageous and superior in representing sexual dimorphism in the pathogenesis of cancer. The main limitation of male-to-female IRRs is their dimensionless scale; thus, sex-specific incidence rates have been considered in concert with this measure to provide the reader with both relative and absolute scales. Although it may also be of interest to assess birth cohort effects of male-to-female IRRs, this was not a primary aim of the analyses described herein.

In conclusion, it is clear that the incidence of many different cancers is higher in males than females. Observing how male-to-female IRRs change with age and period is likely to provide insight for theories of cancer pathogenesis. The pace of these changes alone indicates that the major causes of cancer are environmental. However, the majority of exposures underlying the changes in male-to-female IRRs remain to be elucidated and are, at best, speculative for most cancers. Future epidemiologic studies should be encouraged to design, analyze, and report sex-specific associations to aid our understanding of sex differences in cancer incidence.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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## Sex Disparities in Cancer Incidence by Period and Age

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