Published OnlineFirst October 27, 2009; DOI: 10.1158/1055-9965.EPI-09-0638

Incidence of Carcinoma of the Major Salivary Glands According to the WHO Classification, 1992 to 2006: A Population-Based Study in the United States

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Abstract

Background: **Carcinomas of the major salivary glands (M-SGC) comprise a morphologically diverse group of rare tumors of largely unknown cause. To gain insight into etiology, we evaluated incidence of M-SGC using the WHO classification schema (WHO-2005).**

Methods: **We calculated age-adjusted incidence rates (IR) and IR ratios (IRR) for M-SGC diagnosed between 1992 and 2006 in the Surveillance, Epidemiology and End Results Program.**

Results: **Overall, 6,391 M-SGC (IR, 11.95/1,000,000 person-years) were diagnosed during 1992 to 2006. Nearly 85% of cases (n = 5,370; IR, 10.00) were encompassed within WHO-2005, and among these, males had higher IRs than females [IRR, 1.51; 95% confidence interval (95% CI), 1.43-1.60]. Squamous cell (IR, 3.44) and mucoepidermoid (IR, 3.23) carcinomas occurred most frequently among males, whereas mucoepidermoid (IR, 2.67), acinic cell (IR, 1.57), and adenoid cystic (IR, 1.40) carcinomas were most common among females. Mucoepidermoid, acinic cell, and adenoid cystic carcinomas predominated in females through age ~50 years; thereafter, IRs of acinic cell and adenoid cystic carcinomas were nearly equal among females and males, whereas IRs of mucoepidermoid carcinoma among males exceeded IRs among females (IRR, 1.57; 95% CI, 1.38-1.78). Except for mucoepidermoid and adenoid cystic carcinomas, which occurred equally among all races, other subtypes had significantly lower incidence among Blacks and Asians/Pacific Islanders than among Whites. Adenoid cystic carcinoma occurred equally in the submandibular and parotid glands, and other M-SGC histologic subtypes evaluated had 77% to 98% lower IRs in the submandibular gland. Overall M-SGC IRs remained stable during 1992 to 2006.**

Conclusion: **Distinct incidence patterns according to histologic subtype suggest that M-SGC are a diverse group of neoplasms characterized by etiologic and/or biological heterogeneity with varying susceptibility by gender and race.** (Cancer Epidemiol Biomarkers Prev 2009;18(11):2899–906)

Introduction

Carcinomas of the major salivary glands (M-SGC) are rare malignancies comprising 11% of all oropharyngeal neoplasms in the United States (1). However, in contrast to most head and neck cancers that are predominantly squamous cell carcinomas (1, 2), M-SGC encompass at least 20 distinct histologic subtypes (3). The first classification scheme of salivary gland tumors was proposed by Foote and Frazell (4) with subsequent refinements leading to the most recent WHO classification published in 2005 (WHO-2005; ref. 3). The rarity of M-SGC coupled with its complex and changing classification schema over time has made the diagnosis of M-SGC challenging. Further complicating the classification of salivary gland tumors is the occurrence of salivary gland cancers in the major and minor salivary glands, existence of similarly numerous benign entities, and histologic diversity within the same specimen (5).

Tobacco and alcohol use are major risk factors for cancers of the oral cavity and pharynx, but little is known about the etiology of M-SGC (6). Some studies have suggested a link between M-SGC and occupational exposures, UV light, viruses, tobacco, and alcohol; however, ionizing radiation is the only well-established risk factor (6, 7).

Descriptive studies of cancer incidence can provide insight into etiology. Whereas distinct age-specific patterns may reflect differences in disease biology and/or host susceptibility, variations in temporal trends can reflect changes in exposures, methods of detection/diagnosis, and/or changing classification schemes. Precise histologic diagnoses are important not only for determining prognosis and treatment but also for facilitating identification of risk factors in epidemiologic studies.

Epidemiologic data on M-SGC has been largely based on clinical series (8-12), with some population-based studies describing M-SGC incidence (13-19) but none considering incidence rates (IR) according to histology. Therefore, with the paucity of population-based studies of M-SGC, we used data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program to provide new information on M-SGC incidence in the United States according to histologic subtype. Focusing

Received 6/27/09; revised 8/30/09; accepted 9/1/09; published OnlineFirst 10/27/09.

Grant support: Intramural Research Program of the National Cancer Institute/NIH, Department of Health and Human Services, and Department of Veterans Affairs.

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doi:10.1158/1055-9965.EPI-09-0638

Published OnlineFirst October 27, 2009; DOI: 10.1158/1055-9965.EPI-09-0638

Table 1. Age-adjusted IRs and IRRs of M-SGC diagnosed in SEER-13 according to histology, overall and by gender, 1992 to 2006

	ICD-O-3 codes	Mean/median age (y)		All		Males		Females		Male/female
		Males	Females	*n*	IR	*n*	IR	*n*	IR	IRR (95% CI)
All cases	*	63/65	59/61	6,391	11.95	3,601	15.67	2,790	9.51	1.65 (1.57-1.73)
Total, WHO	*	62/64	58/59	5,370	10.00	2,932	12.62	2,438	8.33	1.51 (1.43-1.60)
Mucoepidermoid carcinoma	8430	58/61	53/54	1,554	2.85	775	3.23	779	2.67	1.21 (1.09-1.34)
Squamous cell carcinoma	8070	72/73.5	74/77	942	1.83	720	3.44	222	0.73	4.70 (4.03-5.49)
Adenoid cystic carcinoma	8200	56/55	56/57	709	1.30	303	1.21	406	1.40	0.86 (0.74-1.00)
Adenocarcinomas										
Acinic cell carcinoma	8550	51/50	49/48	770	1.38	313	1.20	457	1.57	0.77 (0.66-0.89)
Adenocarcinoma-NOS	8140	65/66	65/68	641	1.22	396	1.71	245	0.83	2.06 (1.75-2.42)
Salivary duct carcinoma	8500	65/67	67/66	92	0.18	67	0.29	25	0.09	3.38 (2.10-5.59)
Basal cell adenocarcinoma	8147	62/61.5	66/70	80	0.15	36	0.15	44	0.15	0.98 (0.61-1.56)
Oncocytic carcinoma	8290	71/70	70/75.5	43	0.08	25	0.12	18	0.06	1.94 (1.01-3.77)
Clear cell adenocarcinoma-NOS	8310	65/66.5	70/71	30	0.06	22	0.09	8	~	~
Cystadenocarcinoma	8440	65/60	61/64	23	0.04	17	0.07	6	~	~
Mucinous adenocarcinoma	8480	61/63	50/54	16	0.03	9	~	7	~	~
Polymorphous low-grade adenocarcinoma	8525	65/64	60/62.5	15	~	11	~	4	~	~
Sebaceous carcinoma/lymphadenocarcinoma	8410	51/56	—	3	~	3	~	0	~	~
Mixed tumors										
Carcinoma ex-pleiomorphic adenoma	8941	59/59	64/65	174	0.33	91	0.37	83	0.28	1.31 (0.96-1.78)
Carcinosarcoma	8980	60/60	62/61	15	~	8	~	7	~	~
Other rare carcinomas										
Epithelial-myoepithelial carcinoma	8562	65/66	68/70	96	0.18	39	0.17	57	0.19	0.87 (0.56-1.33)
Lymphoepithelial carcinoma	8082	56/58	60/61	55	0.10	25	0.10	30	0.10	1.00 (0.56-1.76)
Small cell carcinoma	8041	72/74	76/81	45	0.09	32	0.15	13	~	~
Large cell carcinoma	8012	72/73.5	72/73.5	38	0.07	28	0.13	10	~	~
Myoepithelial carcinoma	8982	61/64	63/63	29	0.06	12	~	17	0.06	~
Total, non-WHO	*	67/70	67/69	1,021	1.95	669	3.05	352	1.19	2.58 (2.26-2.94)

NOTE: IRs are age-adjusted to the 2000 U.S. standard population and expressed per 1,000,000 person-years. IRRs are based on unrounded rates.
Abbreviations: ~, IR and IRRs not calculated for <16 cases; —, no cases.
*"All cases" includes ICD-O-3 histology codes in "total, WHO" and "total, non-WHO" categories. "Total, WHO" includes all codes in the specified subcategories and "total, non-WHO" includes all ICD-O-3 codes not specified within "total, WHO" category.

on malignant entities localized in the major salivary glands, we limited our study to more contemporaneously diagnosed cases that would facilitate the use of the WHO-2005 classification schema (3).

Materials and Methods

We evaluated the incidence of M-SGC in 13 population-based cancer registry areas of the SEER Program (SEER-13) during 1992 to 2006 using the Limited-Use Database, November 2008 submission (20). SEER-13 covers ~14% of the United States population and includes the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah and the areas of Detroit, MI; San Francisco, Los Angeles, and San Jose-Monterey, CA; Seattle-Puget Sound, WA; and Atlanta, GA and rural Georgia and also includes cases diagnosed among Alaskan Natives in Alaska. The SEER Program currently classifies information on morphology and topography according to the *International Classification of Diseases for Oncology, Third Edition* (ICD-O-3; ref. 21).

We considered all M-SGC (ICD-O-3 topography codes C07.9 and C08.0-08.9) with malignant behavior diagnosed during 1992 to 2006. All lymphohematopoietic malignancies were excluded from the analysis (n = 1,255) as were cases that were not microscopically confirmed (n = 74). ICD-O-3 histology codes that were specified in the WHO-2005 classification were included in a category entitled "total, WHO" and those histology codes not specified in the WHO-2005 classification were collectively included in a group entitled "total, non-WHO." Specific histology categories were based on the WHO-2005 classification (3), with ICD-O-3 codes as described in Table 1. Except for polymorphous low-grade adenocarcinoma (M-8525) and myoepithelial carcinoma (M-8982), which were introduced with ICD-O-3 in 2000, all other histology codes were included in ICD-O-2 (22).

We estimated age-adjusted IRs, IR ratios (IRR), and annual percent change (APC) in incidence using SEER*-Stat 6.5.1. All IRs were expressed per 1,000,000 person-years and age-adjusted to the 2000 U.S. standard population. IRs were calculated according to histology, race (White, Black, Asian/Pacific Islander, other and unknown), gender (male, female), age at diagnosis (<50, ≥50 or <65, ≥65 years), and site [parotid gland (C07.9), submandibular gland (C08.0), sublingual gland (C08.1), overlapping sites and site not specified (C08.8-C08.9)]. Age-adjusted temporal trends (1992-1996, 1997-2001, 2002-2006) and age-specific IRs (<15, 15-24, 25-34, 35-44, 45-54, 55-64, 65-74, ≥75 years) were plotted on a log-linear scale, where a slope change of 10° approximates a rate change of 1% per year as described previously (23). IRs were not calculated for <16 cases (1).

Results

Overall, 6,391 M-SGC (IR, 11.95/1,000,000 person-years) were diagnosed in SEER-13 during 1992 to 2006 (Table 1). Nearly 85% of cases were encompassed within the WHO-2005 classification (n = 5,370; IR, 10.00), with males having 51% higher IR than females (IRR, 1.51, 95% CI 1.43-1.60). For males and females, mean and median ages at diagnosis

Table 2. Age-adjusted IRs and IRRs of M-SGC diagnosed in SEER-13 according to histologic subtype, 1992 to 2006

	Total, WHO			Mucoepidermoid			Squamous cell			Adenoid cystic			Acinic cell			Adenocarcinoma-NOS			Carcinoma ex-pleiomorphic			Total, non-WHO		
	n	IR	IRR (95% CI)	*n*	IR	IRR (95% CI)	*n*	IR	IRR (95% CI)	*n*	IR	IRR (95% CI)	*n*	IR	IRR (95% CI)	*n*	IR	IRR (95% CI)	*n*	IR	IRR (95% CI)	*n*	IR	IRR (95% CI)
Site																								
Parotid	4,265	7.94	1.00 (reference)	1,326	2.43	1.00 (reference)	796	1.54	1.00 (reference)	323	0.59	1.00 (reference)	736	1.32	1.00 (reference)	486	0.92	1.00 (reference)	134	0.25	1.00 (reference)	824	1.58	1.00 (reference)
Submandibular	845	1.58	0.20 (0.18-0.21)	159	0.29	0.12 (0.10-0.14)	126	0.24	0.16 (0.13-0.19)	327	0.60	1.03 (0.88-1.20)	17	0.03	0.02 (0.01-0.04)	94	0.18	0.19 (0.15-0.24)	31	0.06	0.23 (0.15-0.35)	140	0.27	0.17 (0.14-0.20)
Sublingual	58	0.11	0.01 (0.01-0.02)	24	0.05	0.02 (0.01-0.03)	7	~	~	23	0.04	0.07 (0.04-0.11)	1	~	~	2	~	~	0	~	~	3	~	~
Other/unspecified	202	0.38	0.05 (0.04-0.05)	45	0.08	0.03 (0.02-0.05)	13	~	~	36	0.07	0.11 (0.08-0.16)	16	0.03	0.02 (0.01-0.04)	59	0.11	0.12 (0.09-0.16)	9	~	~	54	0.10	0.07 (0.05-0.09)
Race																								
White	4,394	10.30	1.00 (reference)	1,210	2.82	1.00 (reference)	847	2.01	1.00 (reference)	555	1.29	1.00 (reference)	637	1.47	1.00 (reference)	537	1.27	1.00 (reference)	140	0.33	1.00 (reference)	872	2.06	1.00 (reference)
Black	415	8.13	0.79 (0.71-0.88)	146	2.82	1.00 (0.83-1.19)	49	1.10	0.55 (0.40-0.73)	62	1.22	0.94 (0.71-1.24)	56	0.90	0.61 (0.45-0.81)	49	1.00	0.79 (0.57-1.06)	15	~	~	73	1.53	0.74 (0.57-0.94)
Asian/Pacific Islander	474	8.20	0.80 (0.72-0.88)	169	2.82	1.00 (0.84-1.18)	38	0.74	0.37 (0.26-0.51)	84	1.44	1.11 (0.87-1.41)	65	1.07	0.73 (0.55-0.95)	49	0.87	0.69 (0.50-0.93)	15	~	~	65	1.17	0.57 (0.43-0.73)
Other/unspecified	87	~	~	29	~	~	8	~	~	8	~	~	12	~	~	6	~	~	4	~	~	11	~	~
Age (y)																								
<50	1,513	3.55	1.00 (reference)	574	1.34	1.00 (reference)	51	0.12	1.00 (reference)	258	0.61	1.00 (reference)	387	0.90	1.00 (reference)	106	0.26	1.00 (reference)	45	0.11	1.00 (reference)	156	0.37	1.00 (reference)
≥50	3,857	26.89	7.57 (7.13-8.04)	980	6.81	5.09 (4.58-5.65)	891	6.29	51.42 (38.77-69.63)	451	3.11	5.10 (4.37-5.97)	383	2.65	2.94 (2.54-3.39)	535	3.73	14.61 (11.84-18.17)	129	0.89	8.31 (5.88-11.95)	865	6.09	16.5 (13.86-19.66)
Age and gender																								
<50 y																								
Females	848	3.99	1.00 (reference)	333	1.56	1.00 (reference)	16	0.08	1.00 (reference)	147	0.69	1.00 (reference)	238	1.12	1.00 (reference)	49	0.23	1.00 (reference)	21	0.10	1.00 (reference)	54	0.26	1.00 (reference)
Males	665	3.13	0.78 (0.71-0.87)	241	1.12	0.72 (0.61-0.85)	35	0.17	2.22 (1.20-4.30)	111	0.53	0.76 (0.59-0.98)	149	0.69	0.62 (0.50-0.76)	57	0.28	1.18 (0.79-1.76)	24	0.11	1.11 (0.59-2.10)	102	0.48	1.89 (1.35-2.68)
≥50 y																								
Females	1,590	19.67	1.00 (reference)	446	5.58	1.00 (reference)	206	2.45	1.00 (reference)	259	3.25	1.00 (reference)	219	2.75	1.00 (reference)	196	2.40	1.00 (reference)	62	0.76	1.00 (reference)	298	3.62	1.00 (reference)
Males	2,267	37.46	1.90 (1.78-2.03)	534	8.74	1.57 (1.38-1.78)	685	11.99	4.90 (4.18-5.76)	192	2.98	0.92 (0.76-1.11)	164	2.54	0.92 (0.75-1.14)	339	5.48	2.28 (1.90-2.74)	67	1.04	1.37 (0.95-1.98)	567	9.77	2.70 (2.34-3.12)

NOTE: IRs are age-adjusted to the 2000 U.S. standard population and expressed per 1,000,000 person-years. IRRs are based on unrounded rates.
Abbreviations: ~, IRs and IRRs not calculated for other/unspecified race or <16 cases.

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were younger for cases included in the total WHO category than for those in the non-WHO category. There was marked variation in age at diagnosis ranging from mean/median ages of 51/50 years and 49/48 years for acinic cell carcinoma among males and females, respectively, to mean/median ages of ≥72 years for squamous cell, small cell, and large cell carcinomas among males and females.

When considering the WHO M-SGC subtypes, the highest IRs were observed for squamous cell (IR, 3.44), mucoepidermoid (IR, 3.23), and adenocarcinoma-not otherwise specified (adenocarcinoma-NOS; IR, 1.71) among males. Among females, the highest IRs were noted for mucoepidermoid (IR, 2.67), acinic cell (IR, 1.57), and adenoid cystic (IR, 1.40) carcinomas. Squamous cell, adenocarcinoma-NOS, and salivary duct carcinomas were associated with >2-fold higher incidence among males than among females, whereas acinic cell and adenoid cystic carcinoma had substantially lower IRs among males than among females.

Except for adenoid cystic carcinoma that occurred equally in the submandibular and parotid glands, M-SGC of the submandibular gland had 77% to 98% lower IRs than those diagnosed in the parotid gland (Table 2). Overall IRs of total WHO and non-WHO M-SGC were significantly lower among Blacks and Asians/Pacific Islanders than among Whites. Mucoepidermoid carcinoma occurred equally among Whites, Blacks, and Asians/Pacific Islanders (Black-White IRR, 1.00 and Asian/Pacific Islander-White IRR, 1.00) and similar IRs were also noted for adenoid cystic carcinoma (Black-White IRR, 0.94 and Asian/Pacific Islander-White IRR, 1.11). All histologic subtypes included in Table 2 were more frequent among those ages ≥50 years compared with those ages <50 years; however, a broad range of IRRs were observed from ~3- to 5-fold higher IRs for mucoepidermoid, adenoid cystic, and acinic cell carcinomas to >50-fold IRR for squamous cell carcinoma. Among individuals diagnosed before age 50 years, IRs of mucoepidermoid (IRR, 0.72), adenoid cystic (IRR, 0.76), and acinic cell (IRR, 0.62) carcinomas were significantly lower in males compared with females; in contrast, a 2-fold higher incidence of squamous cell carcinoma (IRR, 2.22) was observed among males than females. Adenoid cystic and acinic cell carcinoma IRs were generally similar among males and females diagnosed at ages ≥50 years, whereas significantly higher IRs of mucoepidermoid and squamous cell carcinomas and adenocarcinoma-NOS occurred among older males compared with older females.

We further explored age-specific differences by gender as depicted in Fig. 1. Mucoepidermoid, adenoid cystic, and acinic cell carcinomas tended to have an earlier age at onset than adenocarcinoma-NOS, squamous cell carcinoma, and carcinoma ex-pleiomorphic adenoma. Mucoepidermoid, adenoid cystic, and acinic cell carcinomas were more common among females through age ~50 years; thereafter, incidence of adenoid cystic and acinic cell carcinomas was nearly equal among females and males at older ages in contrast to mucoepidermoid carcinoma that

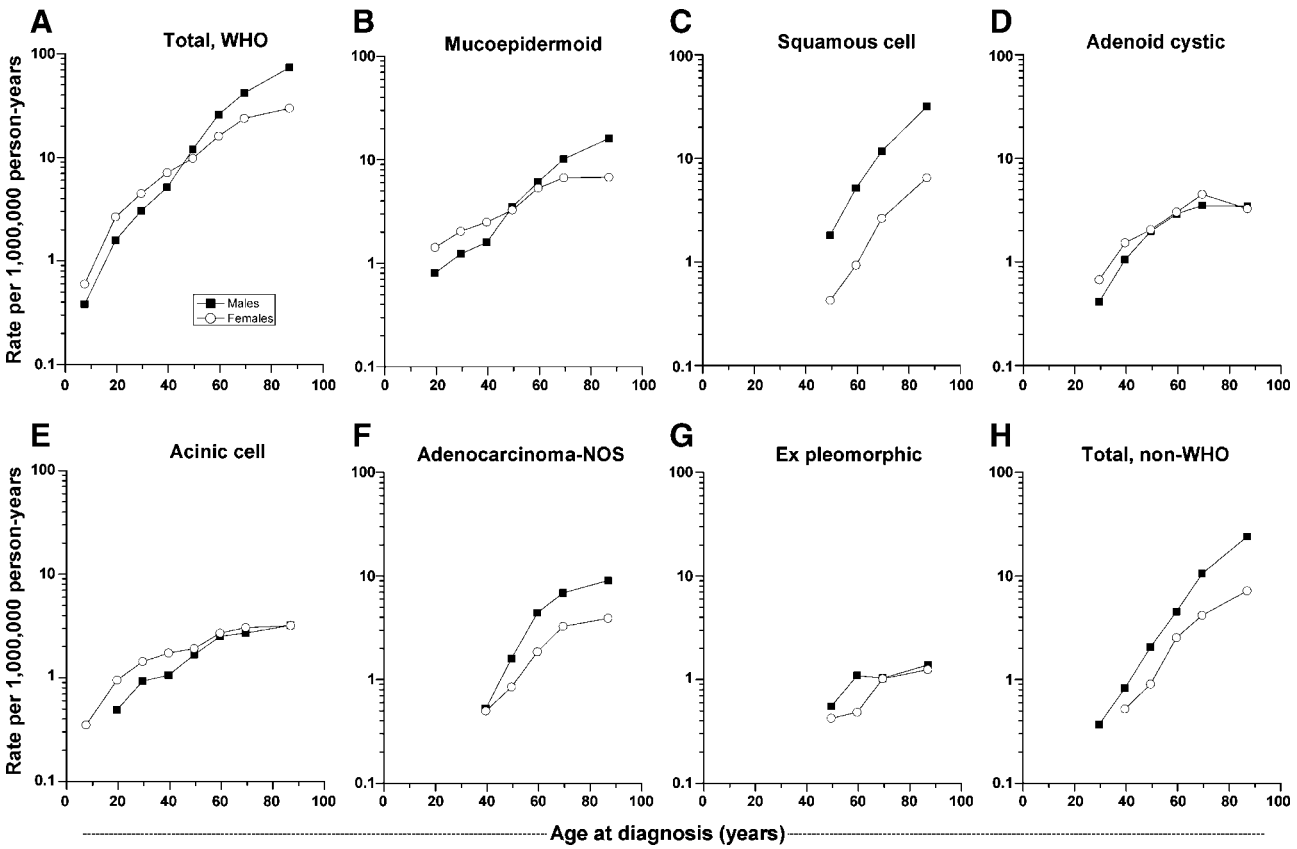

Figure 1. **A** to **H,** age-specific IRs of M-SGC diagnosed in SEER-13 according to histology and gender, 1992 to 2006.

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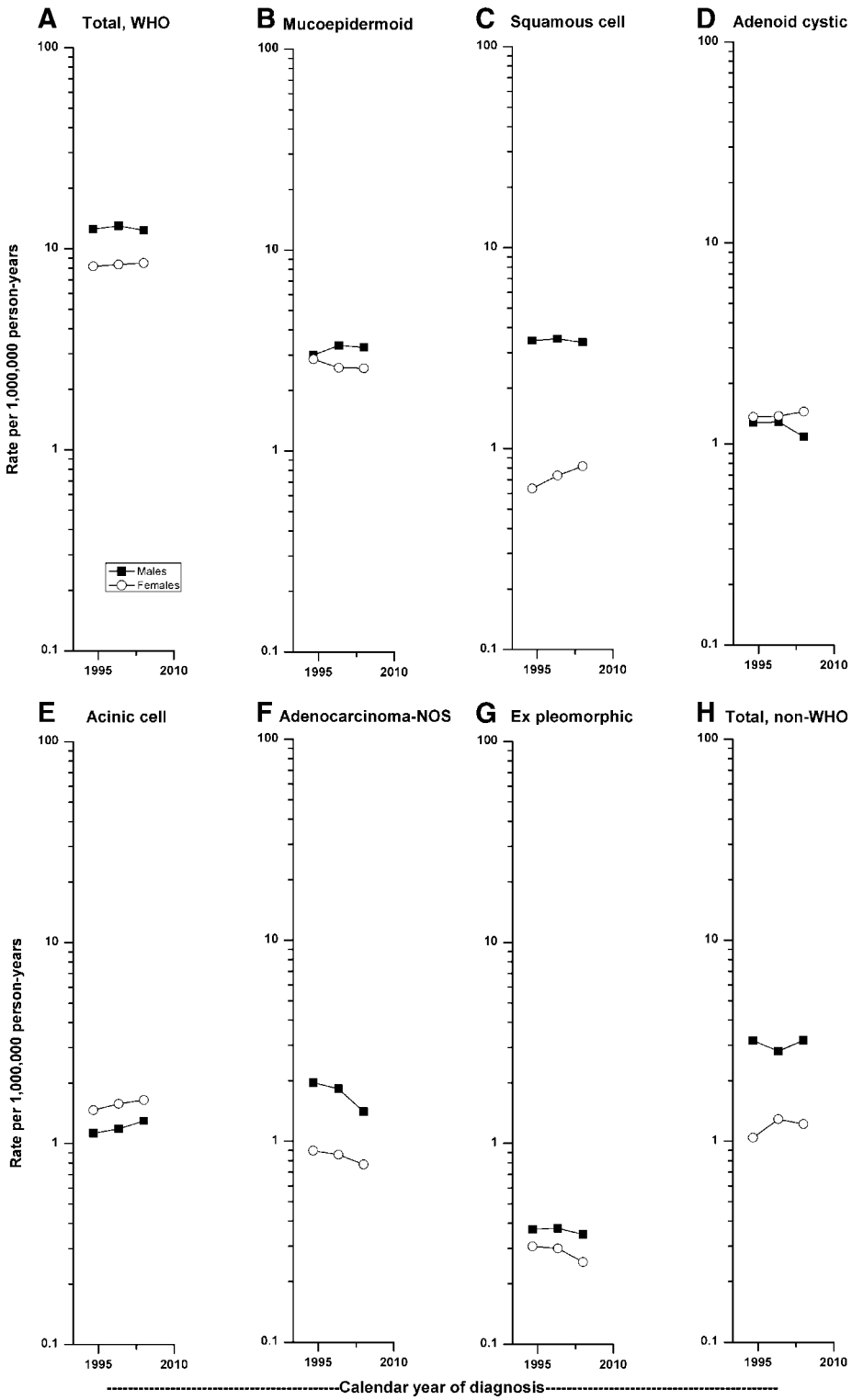

Figure 2. **A** to **H,** trends in age-adjusted IRs of M-SGC diagnosed in SEER-13 according to histology and gender, 1992 to 2006.

had higher IRs among older males than among older females. Mucoepidermoid carcinoma was the only histologic subtype evaluated that was uniquely characterized by a crossing age-specific IR pattern by gender, which was also reflected in the total WHO category. For adenoid cystic and acinic cell carcinomas, IRs increased more prominently at younger ages with a more moderate increase in incidence thereafter among males and females. These patterns

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contrast with the exponential increase in IRs of squamous cell carcinoma and total, non-WHO M-SGC. Distinct from these age-specific patterns, adenocarcinoma-NOS, which generally had higher IRs among males, was characterized by a steep increase in incidence through midlife with a subsequent plateau at older ages.

Over the 15-year period of study, there was little change in incidence of M-SGC among males and females for all WHO subtypes combined (Fig. 2), with APC of −0.10 ($P = 0.84$) and 0.43 ($P = 0.37$), respectively. The most notable change in incidence was observed for adenocarcinoma-NOS (APC = −2.78; $P \leq 0.01$), which declined more notably among males (APC = −3.01; $P = 0.03$) than among females (APC = −1.85; $P = 0.18$). Temporal patterns were also evaluated according to age group (<65, ≥65 years; data not shown) and only adenocarcinoma-NOS changed significantly, with APC of −3.51 ($P = 0.03$) and −2.19 ($P = 0.02$) among those <65 and ≥65 years, respectively. IRs of carcinoma ex-pleiomorphic adenoma also decreased among males and females, although APC was not significant for either (males: APC = −0.42 and females: APC = −1.26). The greatest increase in IR during 1992 to 2006 was noted for squamous cell carcinoma among females (APC = 2.44; $P = 0.14$), in contrast to the slight decrease in IR observed among males (APC = −0.18; $P = 0.80$), particularly in the more recent calendar period. Acinic cell carcinoma was the only M-SGC subtype with slight but progressive increase in IR over time among males and females (males: APC = 0.83; $P = 0.42$ and females: APC = 0.97; $P = 0.47$).

Discussion

This is among the first studies to evaluate patterns of M-SGC incidence in a U.S. population during 1992 to 2006 according to the WHO-2005 classification that presents a detailed evaluation of >6,000 cases by age, gender, race, calendar year, and site. New information includes the observation that the highest IRs among males were observed for squamous cell carcinoma, mucoepidermoid carcinoma, and adenocarcinoma-NOS, whereas the predominant histologic subtypes among females were mucoepidermoid, acinic cell, and adenoid cystic carcinomas. Male-to-female IRRs varied markedly, with 14% to 23% lower incidence for acinic cell and adenoid cystic carcinoma and ~5-fold higher IRR for squamous cell carcinoma. Mucoepidermoid and adenoid cystic carcinomas IRs were similar among Whites, Blacks, and Asians/Pacific Islanders, whereas most other histologic subtypes evaluated generally had higher IRs among Whites. Except for adenoid cystic carcinoma, which developed equally in the parotid and submandibular glands, other subtypes occurred primarily in the parotid gland. Age-specific IRs varied by histologic subtype among males and females, and an age-gender interaction was suggested for mucoepidermoid carcinoma. Incidence of adenocarcinoma-NOS decreased significantly over the 15-year period of study, with no significant changes in other histologic subtypes. Taken together, we show tremendous heterogeneity in M-SGC incidence patterns by WHO-2005 histologic subtypes, suggesting that this rare tumor includes distinct entities associated with etiologic and/or biological diversity.

In contrast to other head and neck cancers that are largely squamous cell histology (1, 2), M-SGC includes numerous histologic subtypes with a classification schema that has evolved over time (4, 8). M-SGC is further distinguished from other head and neck malignancies by its lack of international variation (16), although comparisons across international population-based and clinical series are limited by differences in study inclusion criteria (e.g., benign +/− malignant tumors, major +/− minor salivary glands, varying histologic categories). Furthermore, prior population-based studies have reported frequency distributions of M-SGC according to histologic subtype (13-15, 18, 19), but none have described corresponding IRs.

There are substantial differences across studies regarding frequencies of M-SGC by histologic subtypes. Many series describe mucoepidermoid carcinoma to be the most commonly occurring M-SGC (8, 11, 12, 24, 25); however, others report a predominance of adenoid cystic carcinoma or nearly equal frequencies of adenoid cystic and mucoepidermoid carcinomas (14, 15, 18, 26). In one of the largest series of M-SGC to date (8), the Armed Forces Institute of Pathology reported mucoepidermoid carcinoma as the most common histology followed in turn by acinic cell carcinoma, adenoid cystic carcinoma, adenocarcinoma-NOS, polymorphous low-grade adenocarcinoma, and carcinoma ex-pleiomorphic adenoma. This M-SGC histology distribution differs from that observed in the SEER population. Although the Armed Forces Institute of Pathology series included only data from civilian laboratories in an effort to minimize potential bias related to cases diagnosed among male military personnel (8), the possibility of referral bias of more difficult cases cannot be excluded. In the SEER population, the average age of several M-SGC, including mucoepidermoid, adenocarcinoma-NOS, acinic cell, and squamous cell carcinomas, was generally older than that reported in the Armed Forces Institute of Pathology series, raising the possibility that M-SGC diagnosed among younger individuals may be preferentially sent for external pathology review. Notably, polymorphous low-grade adenocarcinoma was rare in our study, likely reflecting its general occurrence in the minor salivary glands and the absence of an ICD-O histology code until 2000.

Population-based studies of M-SGC that have considered age-specific IR patterns according to gender are rare (17). Findings from another SEER-based study (1973-1992) suggested the presence of an age-gender interaction with predominance of M-SGC among females at younger ages and among males at older ages (17). Considering only histologies within the WHO classification, we show that overall IRs of M-SGC are higher among females compared with males before age ~50 years and that IRs among males exceed those among females at older ages. The resulting age-specific crossing pattern was especially marked for mucoepidermoid carcinoma and is consistent with a qualitative or age-gender interaction (27). These findings raise the possibility that hormonal influences may be important to the development of mucoepidermoid carcinoma and similarly may be central to the development of acinic and adenoid cystic carcinomas that were more common among females at younger ages. Although M-SGC has been linked with reproductive risk factors in at least one study (28), reports have been inconsistent (29).

Ionizing radiation is a well-established risk factor for mucoepidermoid M-SGC in irradiated populations (6, 7). However, radiation likely accounts for only a small fraction of M-SGC reported in our general population study. The

Published OnlineFirst October 27, 2009; DOI: 10.1158/1055-9965.EPI-09-0638

evidence linking M-SGC to occupational exposures is sparse, although elevated risks have been noted among male woodworkers, rubber industry workers, and persons exposed to nickel compounds or silica dust (6). It is plausible that the more prominent increase in incidence of M-SGC at older ages among males compared with females, particularly for mucoepidermoid carcinoma, may reflect occupational exposures in male-dominated jobs, although studies have not assessed risk according to histologic subtypes.

Squamous cell carcinoma accounted for 12% of M-SGC overall and 20% of M-SCG among males. In contrast to our findings, squamous cell carcinomas of the salivary gland generally comprise <10% of cases in other series (8, 10-12, 14, 15). Varying study inclusion criteria may account for some of the differences observed; however, retrospective reviews of cases initially diagnosed as primary squamous cell carcinoma of the salivary gland found that only ~20% of cases were consistent with the original diagnosis (30, 31). In addition, clinical studies evaluating metastases to the parotid glands noted that squamous cell carcinoma accounted for the vast majority of such cases (32, 33). Importantly, a diagnosis of primary squamous cell carcinoma of the salivary gland should be considered only after high-grade mucoepidermoid carcinoma and metastases to the parotid gland from cutaneous, oropharyngeal, or other primary site have been excluded (8, 30, 31, 34).

Although our study cannot determine the extent of possible misclassification of squamous cell carcinomas, the age-specific IR patterns we describe were distinct from those of other specified M-SGC histologic subtypes. The male predominance and the exponential increase in IR of squamous cell carcinoma with advancing age exemplifies IR patterns of cancer sites where the long-term, multistep process of carcinogenesis is deemed important (e.g., lung cancer; ref. 35). When all histologic types are considered jointly, some studies have suggested an association of M-SGC with tobacco use (36, 37), whereas others have found an equivocal relationship (38, 39).

A paucity of data exist on race and M-SGC. Studies from Africa have described a predominance of both mucoepidermoid (25) and adenoid cystic (26) carcinomas. A previous SEER-based study reported 12% to 16% lower IRs of M-SGC among Blacks compared with Whites (40). We found ~20% lower IRs for M-SGC overall among Blacks and Asians/Pacific Islanders compared with Whites; however, no racial predilection was observed for mucoepidermoid and adenoid cystic carcinomas. Although small numbers of cases precluded histology-, gender-, and age-specific analyses by race, our findings suggest that there are racial differences in susceptibility to M-SGC according to histologic subtype.

Similar to results from other series, we found that the majority of M-SGC occurred in the parotid gland (12, 15, 18). The notable exception was adenoid cystic carcinoma, which occurred with equal incidence in the parotid and submandibular glands. These findings further illustrate the diversity that characterizes M-SGC and support the possibility of distinct risk factors and/or biology by histologic subtype.

With the exception of adenocarcinoma-NOS, significant changes in temporal trends were not observed overall or for the other histologic subtypes described. It is possible that the significant decline in incidence for adenocarcinoma-NOS may reflect reclassification to another histologic subtype or a true decline in incidence. Rising temporal trends have been reported previously mainly among older persons (13), suggesting a possible diagnostic bias among the elderly, although findings were limited to males and based on small numbers. In the 15-year period of our study, we did not find IRs to differ significantly by age (<65 versus ≥65 years).

The strengths of our population-based study include the absence of biases inherent to clinical series and the large numbers of histologically confirmed cases of M-SGC. Our analysis is limited by the lack of central pathology review and standardization of histopathologic diagnosis for all reported M-SGC cases. Furthermore, we cannot exclude the possibility of histologic misclassification or misclassified metastatic carcinoma to the salivary gland.

In summary, this investigation is among the first to describe IRs of M-SGC according to histologic categories specified in the most recent WHO-2005 classification schema (3). We show differences in IR patterns of various histologic subtypes of M-SGC according to age, gender, race, and site, and these findings suggest that histologic subtypes of M-SGC are characterized by etiologic heterogeneity and/or differences in disease biology. The marked diversity that exists in this group of carcinomas may account, in part, for the limited understanding of the etiology of these cancers to date. Future studies assessing risk factors and host susceptibility in M-SGC will likely benefit from stratification according to histologic subtype, gender, and race.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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We thank David Check (Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute) for help with the figures.

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Published OnlineFirst October 27, 2009; DOI: 10.1158/1055-9965.EPI-09-0638

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Cancer Epidemiol Biomarkers Prev 2009;18:2899-2906. Published OnlineFirst October 27, 2009.