Gender is an Age-Specific Effect Modifier for Papillary Cancers of the Thyroid Gland

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Abstract

Background: **Thyroid cancer incidence rates have increased worldwide for decades, although more for papillary carcinomas than other types and more for females than males. There are few known thyroid cancer risk factors except female gender, and the reasons for the increasing incidence and gender differences are unknown.**

Methods: **We used the National Cancer Institute's Surveillance, Epidemiology, and End Results 9 Registries Database for cases diagnosed during 1976-2005 to develop etiological clues regarding gender-related differences in papillary thyroid cancer incidence. Standard descriptive epidemiology was supplemented with age-period-cohort (APC) models, simultaneously adjusted for age, calendar-period and birth-cohort effects.**

Results: **The papillary thyroid cancer incidence rate among females was 2.6 times that among males (9.2 versus 3.6 per 100,000 person-years, respectively), with a widening gender gap over time. Age-specific rates were higher among women than men across all age groups, and the female-to-male rate ratio declined quite consistently from more than five at ages 20-24 to 3.4 at ages 35-44 and approached one at ages 80+. APC models for papillary thyroid cancers confirmed statistically different age-specific effects among women and men ($P < 0.001$ for the null hypothesis of no difference by gender), adjusted for calendar-period and birth-cohort effects.**

Conclusion: **Gender was an age-specific effect modifier for papillary thyroid cancer incidence. Future analytic studies attempting to identify the risk factors responsible for rising papillary thyroid cancer incidence should be designed with adequate power to assess this age-specific interaction among females and males.** (Cancer Epidemiol Biomarkers Prev 2009;18(4):1092–100)

Introduction

Thyroid cancer is the most common malignant disease of the endocrine system and the sixth most common cancer among females (1). The age-adjusted incidence rates for thyroid cancers have increased worldwide for decades (2-5), though more among females than males and more for papillary than other histological types (3). There are few known thyroid cancer risk factors except female gender and radiation, and the reasons for the increasing incidence or gender differences are unclear. Understanding the differences in papillary thyroid cancer incidence by gender could inform future analytic studies and intervention strategies. We used the National Cancer Institute's Surveillance, Epidemiology, and End Results program to examine thyroid cancer incidence in the United States, stratified by gender and with a focus upon papillary lesions. We supplemented standard descriptive techniques (age- standardized temporal trends and age-specific incidence rates) with a comparative age-period-cohort analysis (APC) analysis.

The application of APC methods may facilitate the assessment of descriptive data, which can be confounded by age, calendar-period, and/or birth-cohort effects. Age effects reflect age-associated genetic events and/or carcinogenic exposures (6). Calendar-period effects may be observed due to changes in screening practices, diagnostic techniques, or classification definitions. Calendar-effects are ''cross-sectional'' since they span or cut across all age groups and birth-cohorts within a given study period. Birth-cohort effects are longitudinal because they reflect the net impact of risk factors on the incidence rates within one generation or birth cohort (7, 8). Comparison of rates by gender and age across study periods and across birth cohorts may help discern the relative roles of these factors and reveal changes in risk that provide clues for further etiologic research.

Three groups have recently examined time trends in thyroid cancer incidence using SEER data (3, 5).[4,5] Only one

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Table 1. Thyroid cancer incidence in SEER's 9-registry database (1976-2005) by gender

Variable	Overall			Females			Males			Female/Male	95% CI	
	N	Rate	SE	*N*	Rate	SE	*N*	Rate	SE	IRR	LL	UL
Total	44,705	6.4	0.03	33,245	9.2	0.05	11,460	3.6	0.03	2.58	2.52	2.63
Histopathology												
Papillary	35,680	5.1	0.03	27,067	7.5	0.05	8,613	2.6	0.03	2.85	2.78	2.92
Follicular	5,801	0.8	0.01	4,142	1.1	0.02	1,659	0.5	0.01	2.15	2.03	2.28
Medullary	1,193	0.2	0.01	717	0.2	0.01	476	0.1	0.01	1.33	1.18	1.50
Anaplastic	710	0.1	0.00	444	0.1	0.01	266	0.1	0.01	1.22	1.05	1.44
Other/Unknown	1321	0.2	0.01	875	0.2	0.01	446	0.1	0.01	1.71	1.57	1.87
Papillary (N = 35,680)												
Age in years												
0-9	35	0.0	0.01	22	0.0	0.01	13	0.0	0.01	1.77	0.86	3.82
10-19	913	0.8	0.03	766	1.4	0.05	147	0.3	0.02	5.43	4.55	6.53
20-29	4,982	4.3	0.06	4,138	7.2	0.11	844	1.4	0.05	5.01	4.65	5.40
30-39	8,190	7.1	0.08	6,529	11.3	0.14	1,661	2.9	0.07	3.89	3.68	4.11
40-49	7,973	8.3	0.09	6,189	12.8	0.16	1,784	3.8	0.09	3.39	3.21	3.57
50-59	6,266	8.6	0.11	4,509	12.1	0.18	1,757	4.9	0.12	2.44	2.31	2.59
60-69	4,106	7.6	0.12	2,726	9.5	0.18	1,380	5.5	0.15	1.72	1.61	1.84
70-79	2,370	6.4	0.13	1,609	7.5	0.19	761	4.9	0.18	1.53	1.41	1.67
80+	845	4.2	0.15	579	4.4	0.18	266	3.9	0.24	1.12	0.96	1.30
Race												
White	29,704	5.2	0.03	22,350	7.7	0.05	7,354	2.7	0.03	2.84	2.76	2.92
Black	1,750	2.6	0.07	1,410	3.8	0.11	340	1.2	0.07	3.15	2.77	3.58
Other	3,939	6.5	0.11	3,080	9.6	0.18	859	3.2	0.11	2.97	2.74	3.21
Unknown	287	~	~	227	~	~	60	~	~	~	~	~
Registry												
SF-Oakland	5,336	4.7	0.06	4,008	6.8	0.11	1,328	2.4	0.07	2.80	2.63	2.99
Connecticut	4,789	4.9	0.07	3,576	7.0	0.12	1,213	2.6	0.08	2.69	2.52	2.87
Detroit	5,470	4.7	0.06	4,155	6.8	0.11	1,315	2.5	0.07	2.74	2.57	2.92
Hawaii	2,319	7.3	0.15	1,716	10.7	0.26	603	3.9	0.16	2.73	2.48	3.00
Iowa	3,963	4.8	0.08	2,996	7.1	0.13	967	2.4	0.08	2.91	2.70	3.13
New Mexico	2,742	6.3	0.12	2,102	9.3	0.20	640	3.2	0.13	2.93	2.67	3.21
Seattle	5,139	5.0	0.07	3,952	7.6	0.12	1,187	2.5	0.07	3.12	2.92	3.34
Utah	2,972	6.4	0.12	2,296	9.7	0.21	676	3.2	0.13	3.07	2.81	3.36
Atlanta	2,950	4.4	0.08	2,266	6.4	0.14	684	2.3	0.09	2.80	2.55	3.07
SEER Stage												
Localized	21,692	3.1	0.02	17,221	4.8	0.04	4,471	1.4	0.02	3.51	3.39	3.63
Regional	11,855	1.7	0.02	8,459	2.3	0.03	3,396	1.0	0.02	2.25	2.16	2.35
Distant	1,330	0.2	0.01	797	0.2	0.01	533	0.2	0.01	1.27	1.13	1.42
Unknown	803	0.1	0.00	590	0.2	0.01	213	0.1	0.01	2.39	2.03	2.82
Tumor Size (1988+)												
0-1 cm	6,719	1.5	0.02	5,397	2.3	0.03	1,322	0.6	0.02	3.74	3.52	3.98
>1 and ≤2 cm	7,232	1.6	0.02	5,796	2.5	0.03	1,436	0.7	0.02	3.75	3.54	3.98
>2 and ≤4 cm	6,029	1.3	0.02	4,541	1.9	0.03	1,488	0.7	0.02	2.82	2.66	2.99
4+ cm	1,768	0.3	0.01	1,064	0.3	0.01	704	0.2	0.01	1.33	1.21	1.47
Unknown	5,358	1.2	0.02	3,907	1.7	0.03	1,451	0.7	0.02	2.39	2.25	2.54

used APC models,[4] and they found significant age, period, and birth cohort effects for papillary thyroid cancers in both females and males. In this study, we were mainly interested the differential APC effects for papillary thyroid cancer between females and males, using a comparative approach. ''Comparative'' APC models link standard APC analyses with statistical analysis of failure time data for an assessment of the null hypothesis of no difference across levels of a variable, i.e., gender in this case.

Materials and Methods

We used the National Cancer Institute's Surveillance, Epidemiology, and End Results 9 Registries Database, November 2007 Submission (9) to analyze male and female thyroid carcinoma incidence rates from 1976 through 2005. The SEER 9 Registries Database included registries in Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah, and included approximately 10% of the US population.

Invasive thyroid cancer cases were coded using the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) (ref. 10) and were stratified into the four major histological types: papillary carcinoma (ICD-O-3 codes 8050, 8260, 8340-8341, 8343-8344, 8350), follicular carcinoma (ICD-O-3 codes 8290, 8330-8332, 8335), medullary carcinoma (ICD-O-3 codes 8345-8346, 8510), and anaplastic carcinoma (ICD-O-3 codes 8012, 8020-8021, and 8030-8032); all other ICD-O-3 codes were categorized as other or unknown.

In addition to gender and histologic type, we evaluated demographic and tumor characteristics including age at diagnosis, race, SEER historic stage A, and tumor size. Racial groups included Whites, Blacks, and other (American Indian, Alaskan Natives, Asians, and Pacific Islanders combined) or unknown race. SEER historic stage A was used to classify thyroid

cancers as localized (limited to the thyroid gland), regional (limited to surrounding tissues), and distant or systemic disease (10). SEER collected all demographic and tumor variables from 1973 forward, except for tumor size. Beginning in 1988, SEER systematically collected information on tumor size, that is the cancer's greatest diameter as recorded on surgical pathology reports. We categorized tumor size as ≤1 cm, >1 cm and ≤2 cm, >2 cm and ≤4 cm, and greater than 4 cm based on the Extent of Disease- 10 (EOD-10) codes for 1988-2003 and the Collaborative Staging (CS) codes for 2004 and 2005 (10).

Data Analysis. Incidence rates (IR) were calculated using SEER*Stat 6.4.4 (11) and expressed per 100,000 person-years, man-years, or woman-years. Age-adjusted rates were standardized to the 2000 US population. Relative risks were expressed as incidence rate ratios (IRR), where a given characteristic was compared to a referent rate with an assigned IRR of 1.0. Statistical significance of rates and IRR were assessed at the $P < 0.05$ alpha level; all hypothesis tests were two-sided.

We divided the 1976 to 2005 study period into either six 5-year calendar-periods (1976-80, 1981-85, 1986-90, 1991-95, 1996-2000, and 2001-05) or three 10-year calendar-periods (1976-85, 1986-95, and 1996-2005). Temporal trends were expressed as the percentage change (%CH = 100 × [final IR-initial IR] / initial IR) from 1976-85 to 1996-2005 (or 1988-95 to 1996-2005 for tumor size); 95% confidence limits were calculated with the delta method for men and women separately (12). Age-adjusted temporal trends and age-specific incidence rates were plotted on a log y and linear × scale, such that a slope of 10 degrees approximated a change in rates of 1% per year (13).

APC models simultaneously assessed the effects of age at diagnosis, calendar period of diagnosis, and year of birth (7, 8, 14-16). Given the relationship [birth cohort] = [calendar-period] minus [age at diagnosis], we had eighteen 5-year birth cohorts (1896 to 1980, referred to by the mid-year of birth) calculated from six 5-year calendar periods (1976-80, 1981-85, . . .2001-05) and thirteen 5-year age groups (ages 20-24, 25-29, . . . 80-84 years). The assumption of APC analysis is that the population-based rates have a log-linear relationship and Poisson distribution for age, period, and cohort effects:

$$\rho_{ij} = \alpha_i + \pi_j + \gamma_k.$$

Here, p_{ij} is the expected log rate over the age groups α_i, calendar-periods π_j, and birth-cohorts γ_k.

Owing to the linear APC relationship, the separate or independent effects of age, period, and cohort cannot be estimated or determined; this is called the non-identifiability problem of APC analysis. Notwithstanding the well-established non-identifiability issue, certain APC parameters can be estimated if the age, period, and cohort effects are orthogonally decomposed into their linear and non-linear components, following the method of Holford (15). The estimable APC parameters included ''drifts'' (7), ''deviations'' (15), ''curvatures'' (8), and ''slope contrasts'' (16).

APC deviations reflect the non-linear departures from their respective linear trends. Net drift is the linear trend in the logarithm of the age-specific rates over time and is equal to the summation of the period and cohort slopes, i.e., $(\pi_L + \gamma_L)$, where π_L and γ_L are the linear trends for calendar-period and birth-cohort effects, respectively. The net drift is estimable (identifiable) even though the constituent components π_L and γ_L are not. Differences in the net drifts were used to test for differential temporal trends. Another type of drift parameter is the longitudinal age trend (LAT). The longitudinal age trend is the linear trend in the logarithm of the age-specific rates across age and is equal to the summation of the age and period slopes, i.e., $(\alpha_L + \pi_L)$, where α_L and π_L are the linear trends for age and period, respectively. Differences in the net drifts were used to test for differential temporal trends. Differences in the longitudinal age trends were used to test for differential age-related effects for the study period.

Another useful APC function is the ''fitted'' age-at-onset curve, as recently introduced (17):

$$\hat{\rho}_i = \mu + (\alpha_L + \pi_L)(i - \bar{i}) + \tilde{\alpha}_i$$

The parameter $\hat{\rho}_i$ reflects the age-specific incidence rate curve after adjustment for calendar-period and birth-cohort deviations; and approximates the true age-specific incidence rate curve devoid of period and/or cohort factors. In this model μ is the intercept term, $(\alpha_L + \pi_L)$ is the longitudinal age trend, and $\tilde{\alpha}_i$ is the age deviation over interval i.

Results

Thyroid cancer incidence rates by histologic type and papillary thyroid cancer incidence rates by demographic and tumor characteristics and female-to-male incidence rate ratios are shown in Table 1. Approximately 80% of all thyroid cancers were the papillary type, 13% were follicular, <3% were medullary, <2% were anaplastic, and 3% were the other/unknown type. Over the entire 30-year calendar period 1976-2005, the rate among females was 2.6 times that among males (female-to-male IRR_{FM} = 2.58; 2.52-2.63); the IRR_{FM} for papillary thyroid cancer was higher (2.85 overall). Over the entire period, the IRR_{FM} for papillary thyroid cancer decreased from more than 5.0 among those aged 10-19 and 20-29 years to 1.1 at ages 80+ years. Rates were higher among Whites than Blacks and highest among other races, which included Asians and/or Pacific Islanders and Native Americans. Among females and males, most thyroid cancers were small (<2.0 centimeters) and were usually diagnosed at the localized stage. Rates for all races combined were highest in Hawaii, followed by Utah and New Mexico, and lowest in Atlanta.

Thyroid cancer incidence rates rose over the time period 1976-2005 among men and women for the papillary type in particular (Table 2A and B). Papillary carcinoma rates doubled, and the small decline in other/unknown types could have played only a very minor role. Papillary cancer rates rose over time in every age group except ages 0-9 years for both men and women; and rates more than doubled among those aged 40-79 years. The increases were more rapid for females than males, for Whites than Blacks or other races, and for

Table 2.

A. Thyroid Cancer Incidence in Women in SEER's 9-Registry Database (1976-2005); percentage change over time

Calendar-period	1976-85			1986-95			1996-2005			%CH 1976-85 or 1988*-95 to 1996-2005		
Variable	*N*	Rate	SE	*N*	Rate	SE	*N*	Rate	SE	%CH	LL	UL
Total (*N* = 34,850)	6,953	6.6	0.08	9,508	7.8	0.08	16,784	12.1	0.09	83.9%	70.7%	76.6%
Histopathology												
Papillary	5,088	4.8	0.07	7,611	6.3	0.07	14,368	10.4	0.09	117.5%	108.4%	127.4%
Follicular	1,196	1.2	0.03	1,287	1.1	0.03	1,659	1.2	0.03	2.9%	2.8%	3.1%
Medullary	213	0.2	0.02	219	0.2	0.01	285	0.2	0.01	-1.0%	-85.9%	-1.1%
Anaplastic	154	0.1	0.01	131	0.1	0.01	159	0.1	0.01	-26.5%	-23.5%	-29.9%
Other/Unknown	388	0.4	0.02	475	0.4	0.02	806	0.6	0.02	47.7%	42.9%	53.0%
Papillary (*N* = 28,180)												
Age in years												
0-9	9	~	~	4	~	~	9	~	~	~	~	~
10-19	216	1.2	0.08	238	1.5	0.10	312	1.7	0.10	46.5%	39.0%	55.5%
20-29	1,169	5.9	0.17	1,261	6.5	0.19	1,708	9.3	0.23	57.5%	51.5%	64.2%
30-39	1,219	7.5	0.22	2,041	9.8	0.22	3,269	15.6	0.27	107.1%	89.3%	128.6%
40-49	882	7.7	0.26	1,634	10.2	0.25	3,673	17.4	0.29	125.1%	98.3%	159.2%
50-59	738	6.7	0.25	1,070	9.9	0.31	2,701	17.4	0.34	158.0%	115.4%	216.4%
60-69	479	5.2	0.24	769	7.8	0.28	1,478	15.1	0.39	188.4%	124.7%	284.8%
70-79	274	4.6	0.28	438	5.9	0.28	897	11.2	0.37	144.1%	96.7%	214.8%
80+	102	3.1	0.31	156	3.6	0.29	321	5.8	0.32	83.9%	59.0%	119.2%
Race												
White	4,300	4.8	0.08	6,287	6.4	0.08	11,763	11.1	0.10	130.8%	118.6%	144.3%
Black	228	2.4	0.17	362	3.0	0.17	820	5.3	0.19	124.2%	91.3%	168.8%
Other	530	8.2	0.38	918	8.9	0.30	1,632	10.6	0.27	29.3%	26.5%	32.3%
Unknown	30	~	~	44	~	~	153	~	~	~	~	~
SEER Stage												
Localized	3,210	3.1	0.06	4,479	3.7	0.06	9,532	6.9	0.07	124.7%	114.0%	136.5%
Regional	1,589	1.5	0.04	2,612	2.1	0.04	4,258	3.1	0.05	111.9%	101.9%	122.9%
Distant	177	0.2	0.01	261	0.2	0.01	359	0.3	0.01	64.3%	53.8%	76.9%
Unknown	112	~	~	259	~	~	219	~	~	~	~	~
Tumor Size (1988+)												
0-1 cm	~	~	~	1,213	1.2	0.04	4,184	3.0	0.05	144.9%	128.8%	163.2%
>1 and ≤2 cm	~	~	~	1,845	1.9	0.04	3,951	2.9	0.05	53.3%	50.2%	56.5%
>2 and ≤4 cm	~	~	~	1,446	1.4	0.04	3,095	2.2	0.04	54.7%	51.3%	58.3%
4+ cm	~	~	~	281	0.2	0.01	783	0.6	0.02	150.7%	124.0%	183.1%
Unknown	5,088	~	~	2,826	~	~	2,355	~	~	~	~	~

B. Thyroid Cancer Incidence in Men in SEER's 9-Registry Database (1976-2005); percentage change over time

Calendar-period	1976-85			1986-95			1996-2005			%CH 1976-85 or 1988*-95 to 1996-2005		
Variable	*N*	Rate	SE	*N*	Rate	SE	*N*	Rate	SE	%CH	LL	UL
Total (*N* = 12,109)	2,591	2.9	0.06	3,378	3.2	0.06	5,491	4.3	0.06	52.0%	49.2%	54.8%
Histopathology												
Papillary	1,797	1.9	0.05	2,447	2.3	0.05	4,369	3.4	0.05	77.8%	72.3%	83.8%
Follicular	455	0.5	0.03	557	0.5	0.02	647	0.5	0.02	2.1%	2.0%	2.3%
Medullary	131	0.1	0.01	150	0.1	0.01	195	0.2	0.01	6.8%	5.9%	7.9%
Anaplastic	72	0.1	0.01	90	0.1	0.01	104	0.1	0.01	-3.1%	-2.6%	-3.7%
Other/Unknown	167	0.2	0.02	245	0.3	0.02	371	0.3	0.02	48.1%	41.0%	56.5%
Papillary (*N* = 9,045)												
Age in years												
0-9	6	~	~	2	~	~	5	~	~	~	~	~
10-19	53	0.3	0.04	36	0.2	0.04	58	0.3	0.04	7.9%	6.0%	10.4%
20-29	241	1.2	0.08	260	1.3	0.08	343	1.8	0.10	47.3%	39.9%	56.1%
30-39	414	2.6	0.13	509	2.5	0.11	738	3.5	0.13	31.8%	28.5%	35.4%
40-49	305	2.8	0.16	487	3.1	0.14	992	4.8	0.15	73.2%	61.5%	87.1%
50-59	336	3.2	0.18	420	4.1	0.20	1,001	6.7	0.21	110.9%	86.4%	142.5%
60-69	269	3.5	0.21	422	5.0	0.24	689	7.9	0.30	128.2%	91.9%	178.8%
70-79	123	3.0	0.27	244	4.5	0.29	394	6.5	0.33	116.4%	76.6%	176.8%
80+	50	3.1	0.45	67	3.2	0.39	149	4.8	0.40	53.9%	37.4%	77.5%
Race												
White	1,487	1.8	0.05	2,113	2.3	0.05	3,754	3.7	0.06	98.8%	89.7%	108.7%
Black	63	0.9	0.12	93	1.0	0.11	184	1.6	0.13	80.6%	57.3%	113.5%
Other	236	4.4	0.31	227	2.8	0.20	396	3.1	0.16	-30.3%	-27.1%	-33.9%
Unknown	11	~	~	14	~	~	35	~	~	~	~	~
SEER Stage												
Localized	960	1.0	0.04	1,174	1.1	0.03	2,337	1.8	0.04	75.4%	69.1%	82.3%

(*Continued on the following page*)

Table 2. (Cont'd)

B. Thyroid Cancer Incidence in Men in SEER's 9-Registry Database (1976-2005); percentage change over time

Calendar-period	1976-85			1986-95			1996-2005			%CH 1976-85 or 1988*-95 to 1996-2005		
Variable	*N*	Rate	SE	*N*	Rate	SE	*N*	Rate	SE	%CH	LL	UL
Regional	665	0.7	0.03	1,051	1.0	0.03	1,680	1.3	0.03	87.2%	78.4%	97.0%
Distant	126	0.1	0.01	140	0.1	0.01	267	0.2	0.01	60.9%	49.7%	74.6%
Unknown	46	~	~	82	~	~	85	~	~	~	~	~
Tumor Size (1988+)												
0-1 cm	~	~	~	318	0.4	0.02	1,004	0.8	0.03	114.4%	98.1%	133.5%
>1 and ≤2 cm	~	~	~	436	0.5	0.02	1,000	0.8	0.02	58.7%	52.8%	65.2%
>2 and ≤4 cm	~	~	~	479	0.5	0.02	1,009	0.8	0.03	49.0%	44.4%	54.2%
4+ cm	~	~	~	202	0.2	0.01	502	0.4	0.02	107.9%	88.5%	131.5%
Unknown	1,797	~	~	1,012	~	~	854	~	~	~	~	~

NOTE: [A] Key: *N*, number of cases; Rate per 100,000 woman-years (age-adjusted to the 2000 US standard population); SE, standard error; %CH, percentage change in rates; LB, UB, 95% lower and upper limits, respectively; ~, not calculated, not applicable, or <10 cases. [B] Key: *N*, number of cases; Rate per 100,000 man-years (age-adjusted to the 2000 US standard population); SE, standard error; %CH, percentage change in rates; LB, UB, 95% lower and upper limits, respectively; ~, not calculated, not applicable, or <10 cases.
*For tumor size, the percent change reflects the change from 1988-95 to 1996-2005.

the smallest and largest tumor sizes compared to those size >1 cm and ≤4 cm.

From 1976-80 to 2001-05, age-adjusted papillary thyroid cancer rates rose 158% from 4.7 to 12.1 per 100,000 among females and rose 106% from 1.9 to 3.9 per 100,000 among males (Fig. 1A). However, rates changed little until after 1985 among females and 1990 among males. From 1990-94 to 2000-04, rates rose 80% among females and 61% among males. The age-specific incidence rate patterns during 1976-2005 differed among females and males, with an early age-at-onset predominance for females (Fig. 1B). That is, incidence rates rose rapidly with increasing age among females, peaking at ages 40-49 years with a rate of 12.8 per 100,000 woman-years then declined to 4.4 per 100,000 at ages 80+ years. In contrast, age-specific rates among males rose more slowly, peaking at ages 60-69 years with a rate of 5.5 per 100,000 man-years then declined to 3.9 per 100,000 at ages above 80 years.

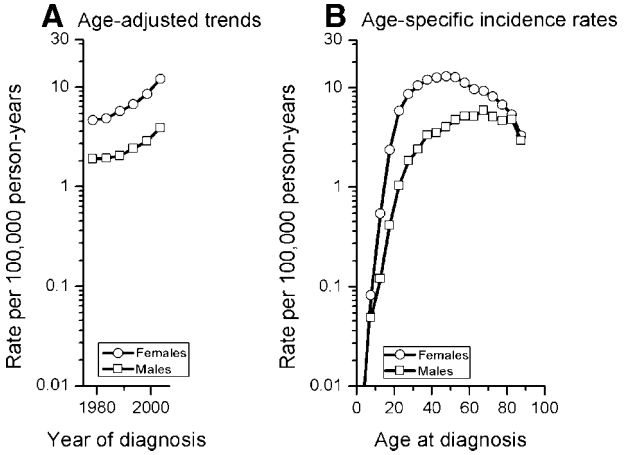

Figure 1. Papillary thyroid cancer incidence rates in the SEER 9 database by gender. **A.** Age-adjusted trends, 1976-80 to 2001-05. **B.** Age-specific incidence rates for females and males during 1976-2005 in the SEER 9 database.

To further evaluate differences in papillary carcinoma rates over time and by age among men and women (Fig. 1A-B), we stratified age-specific incidence rates by gender and calendar period of diagnosis (Fig. 2A-B) as well as by gender and birth cohort (Fig. 2C-D). Among females, period-specific age-specific rates rose rapidly until approximately ages 45-49 years and then fell (Fig. 2A). Among males in all time periods, age-specific rates rose among males until ages 60-65 years before declining (Fig. 2B). In contrast to the difference age-specific patterns by gender, the incidence rates increased rapidly with age for all but the oldest age groups among all cohorts for both females and males (Fig. 2C and D).

Age, period, and cohort effects by gender for papillary thyroid cancer incidence in the period 1976-2005 were further assessed with APC models. Comparing women and men, the age deviations (*P* for the null hypothesis of no difference = 0.39), period deviations (*P* for difference = 0.86), and cohort deviations (*P* for difference = 0.80) were similar. However, irrespective of similar gender-related deviations, the APC longitudinal age trends (LAT) and net drifts were very different among women and men, as were the ''fitted'' age-at-onset curves and ''fitted'' age-specific temporal trends (Fig. 3). For example, the LAT rose at a rate of 3.56% (95% CI; 3.36%, 3.76%) per year of attained age among women, whereas the LAT was 5.02% (95% CI; 4.66%, 5.44%) among men. Consequently, the APC fitted age-at-onset curve (that was adjusted for period and cohort factors) also rose more steadily with advancing age among men than women, which is consistent with the cross-sectional age-specific incidence rates that were not adjusted for period and cohort effects (Fig. 1B). Consequently, the female to male age-specific incidence rate ratio (IRR_{FM}) declined steadily with age in all time periods. Indeed, IRR_{FM} fell more than five at ages 20-24 to 3.4 at ages 35-44 and approached one at ages 80+ (Fig. 4). Of note, advancing age appeared to impact the cross-sectional (Fig. 1B) more than the fitted age-specific rates (Fig. 3A), likely due to period and/or cohort effects. This phenomenon is observed when there is progressive increase in cancer risk from one period and/or one generation to the next (18). By removing these period and/or cohort trends, the fitted curves provided

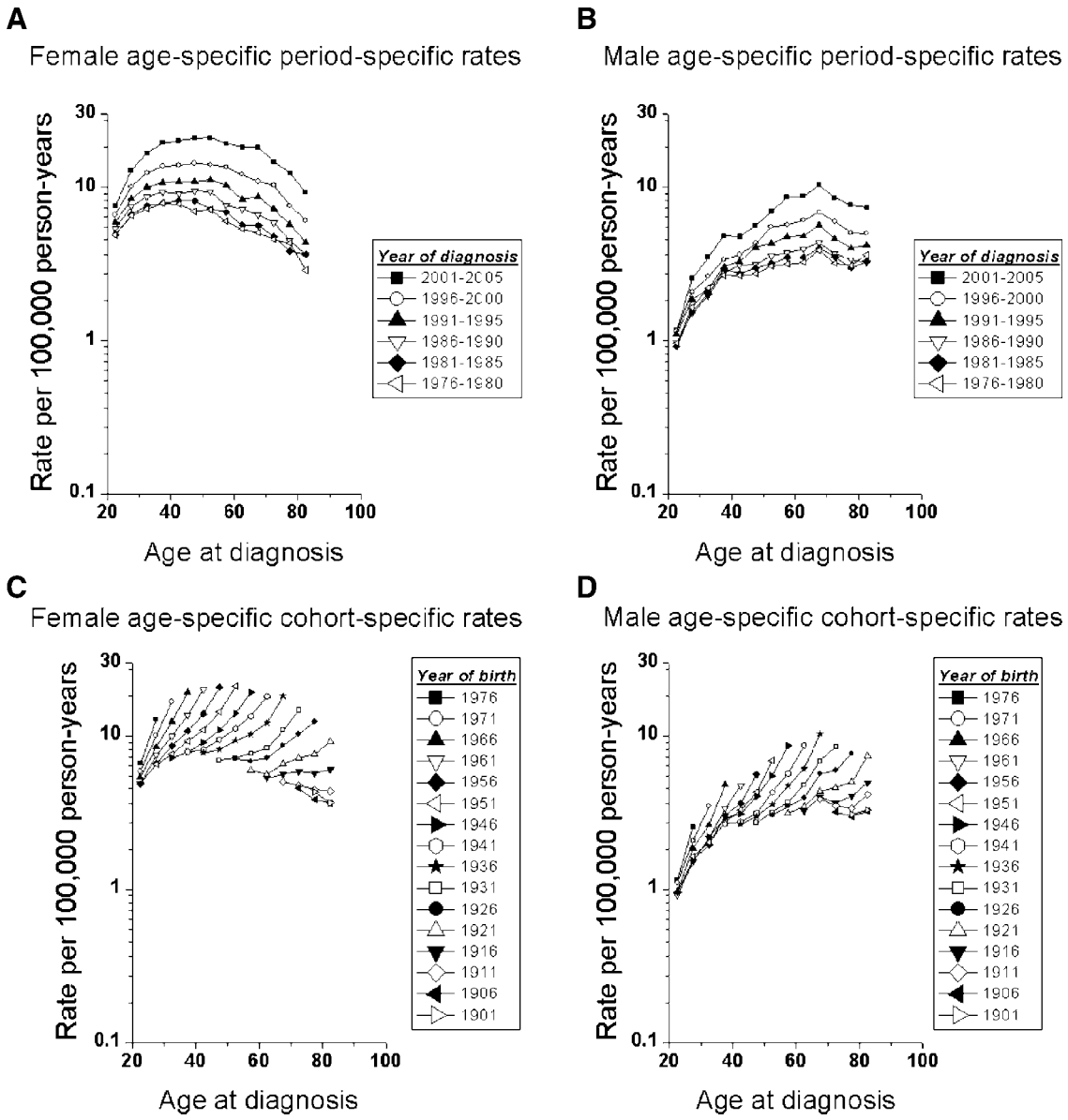

Figure 2. Age-specific incidence rates for females and males by calendar period and birth cohort (SEER 9: 1976-2005). **A.** Female rates stratified by calendar period year of diagnosis. **B.** Male rates stratified by calendar period year of diagnosis. **C.** Female rates stratified by cohort year of birth. **D.** Male rates stratified by cohort year of birth.

estimates of the cross-sectional age-specific incidence rate curves free of secular tends.

Whereas the LATs were greater for men than women, the net drifts were greater for women and men (Fig. 3). For example, the net drift rose at a rate of 4.2% (95% CI; 4.0%, 4.4%) per year of diagnosis among women, whereas the net drift was 3.0% (95% CI; 2.1%, 3.4%) per year of diagnosis among men. Consequently, the age-specific temporal trends rose more steadily for all age groups among women than men, which is consistent with the age-adjusted temporal trend (Fig. 1A). In a sensitivity analysis, we observed similar age-specific effects and secular trends among women and men with small (≤2.0 centimeters) and large (>2.0 centimeters) papillary thyroid cancers, data not shown. That is, irrespective of tumor size, LATs were greater for men than women while net drifts were greater for women than men.

Discussion

In the United States, thyroid cancer incidence has risen steadily for decades, with an increase of 74% from 1976-1985 to 1996-2005. The rise has been largely limited to the papillary histopathological subtype. Papillary carcinoma rates rose in all age groups except the very young, among both blacks and whites, and

for all tumor sizes and all stages of disease, and these increases were more rapid among females than males. Indeed, we found statistically significant temporal and age-related differences for females and males. Gender-related differences (age-adjusted and age-specific incidence rates) were robust in age-period-cohort (APC) models that were simultaneously adjusted for age, period, and cohort effects. For example, at the end of our study period in 2005, age-adjusted incidence rates among females were approximately 3 times those among males, and the APC net drifts over the period 1976-2005 were 40% higher for females (4.2% per year) than for males (3.0% per year). Age-related gender differences were manifested as early-onset predominance among females. In sum, secular trends were greater for females (summarized in the net drifts), whereas the age-related trends were greater for males (summarized in the longitudinal age trends). All in all, these results suggest that gender is an effect modifier of papillary thyroid cancer over time and across age.

Diagnostic sensitivity and opportunities for detection have improved over the past decades with the introduction of thyroid ultrasound in the early 1980s and final-needle aspiration technology in the late 1980s; these technologies could have potentially impacted the secular trends more in one gender than the other. Compared to males, papillary thyroid cancer incidence rates started higher among younger females and rose faster, culminating in a larger net drift among females. A potential explanation for the rapid increase in incidence observed among females occurring early in life may be greater detection during annual obstetrical and gynecological examinations during the reproductive years, whereas the slower rise in incidence among males might reflect more frequent medical visits later in life. Although consensus guidelines do not advocate universal thyroid function screening during pregnancy (19, 20), thyroid testing has become routine in nearly half of prenatal care practices in some areas of the United States (21). Furthermore, while thyroid ultrasound has traditionally been performed in the radiology department, it is increasingly performed in the physician's office. Increases in office-based use of ultrasound may increase the number of thyroid cancers identified, which may also explain some of the interaction with gender.

However, enhanced clinical detection (particularly among females) may not be the sole explanation for differential secular trends among females and males. Increased diagnostic scrutiny would enhance the detection of small tumors (3), whereas our results show significant increases for all tumor sizes. Furthermore, there was a differential gender effect among large as well as small tumors. Consequently, although the combination of the ability to detect and aspirate small nodules has clearly facilitated the diagnosis of smaller thyroid cancers, this does not seem to account for the substantial increases of larger tumors. However, a large proportion of tumor sizes were classified as unknown in the SEER 9 database and this subsequently suggests that though intriguing, these results should be reexamined in future studies with comprehensive tumor size ascertainment.

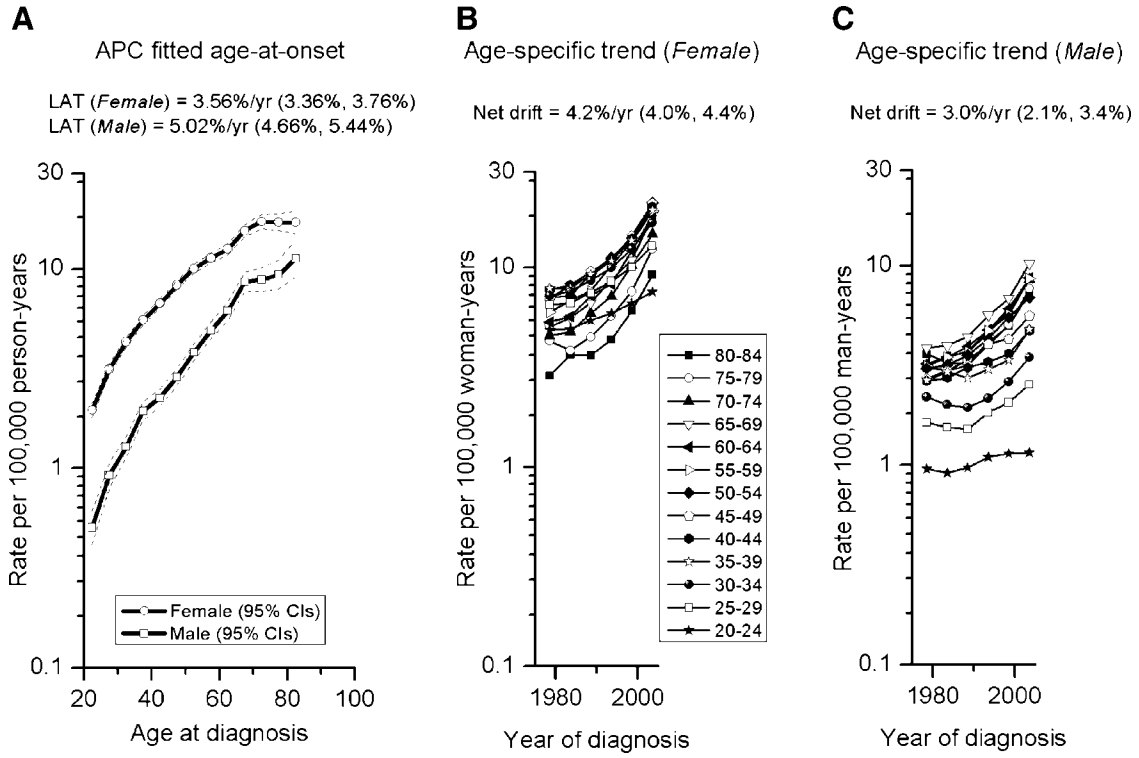

Figure 3. APC fitted age-at-onset curves and age-specific trends for females and males. **A.** Fitted age-at-onset curves derived for females and males with papillary thyroid cancer from 1976-2005. **B.** Age-specific temporal trends and net drift among females. **C.** Age-specific temporal trends and net drift among males. See text for further details.

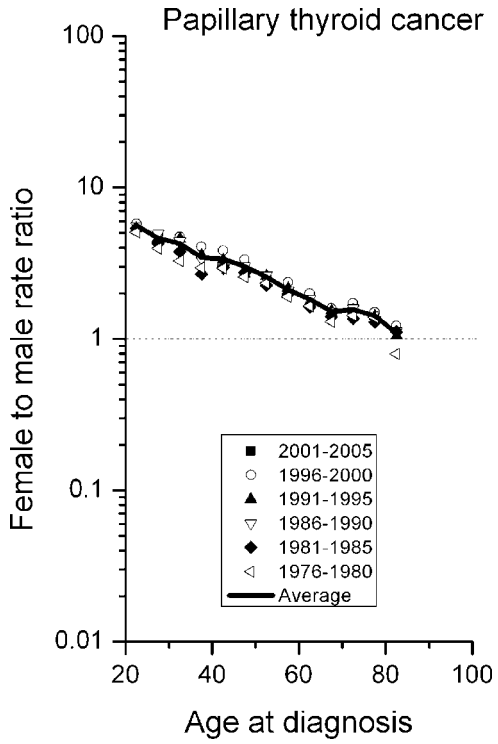

Figure 4. Age-specific female-to-male incidence rate ratios (IRR_{FM}) for the periods of diagnosis, 1976-80 to 2001-05, and the average over the six 5-year periods.

The results of our age-specific analyses also suggest that differential age-related exposures by gender should also be pursued in future analytical studies. Most notable is the female predominance, which is greatest at the younger ages and has been observed worldwide (22). It is also noteworthy that the greatest percent change in incidence over time were observed among females in the older age groups. However, the overall epidemiological evidence of the relationship between reproductive risk factors has been inconsistent and weak (23-27). The age-specific female-to-male rate ratios did not show notable changes around the menopausal years that would suggest a role of changing hormonal exposures. That is, there was a constant decline in the rate ratio with age, although the ratios were similar at ages 35-39 and 40-44 (3.4) and at ages 65-69 to 75-79 (1.4 to 1.6). Possibly, a better understanding of gender-related differences in thyroid stimulating hormone, thyroid biology, and thyroid development may confer important etiological clues.

Our study was limited by the usual concerns related to analyses of registry data: non-review of histopathologic diagnoses, potential incomplete data collection, and inconsistencies in tumor classification over time due to changing staging systems. Our descriptive results are consistent with other population-based studies. However, where other studies have relied largely on standard descriptive techniques, we have supplemented secular trends and age-specific incidence patterns with both traditional and comparative APC analysis, adjusting simultaneously for age, period, and cohort effects and/or artifacts.

In sum, gender was an age-related effect modifier for papillary thyroid cancer, with differential secular trends and age-specific incidence rates among females and males. Given similar age, period, and cohort deviations, the differences between male and female thyroid cancer incidence patterns appears to be largely related to linear trends over time (net drifts) and age (longitudinal age trends). This is of special interest since these drift parameters are often considered nuisance factors when interpreting parameter estimates for a single group. The combination of differential secular and age-related linear trends for papillary thyroid cancer suggests a complex interaction between different temporal (period and/or cohort) and age-related biological factors among females and males. Future analytic studies attempting to identify the risk factors responsible for rising papillary thyroid cancer incidence should be designed with adequate power to assess age-specific interactions between females and males.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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