Research Article

Cancer Epidemiology, Biomarkers & Prevention

Contribution of Demographic and Behavioral Factors on the Changing Incidence Rates of Oropharyngeal and Oral Cavity Cancers in Northern California

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Abstract

Background: It is unknown to what extent patient demographics, smoking, and alcohol use have contributed to changes in oropharyngeal and oral cavity cancer incidence rates.

Methods: We performed a cohort study of Kaiser Permanente healthplan members, ages 20 to 89, for years 1995–2010 ($n = 2.2$ million annual members). Poisson Regression models estimated calendar trends in cancer rates both adjusted for and stratified by age, sex, smoking, and alcohol abuse history.

Results: We identified 1,383 human papillomavirus (HPV)–related and 1,344 HPV-unrelated oral cavity and oropharyngeal cancer cases. With adjustment for age and sex, HPV-related cancer incidence rates increased 3.8% per year ($P < 0.001$) between 1995 and 2010, whereas rates for HPV-unrelated cancers decreased 2.4% per year ($P < 0.001$). For years 2007 to 2010, with additional adjustment for smoking and alcohol abuse, results were nonsignificant, but similar in magnitude. The increasing rates for HPV-related cancers were more prominent among nonsmokers (+14.5%) compared with smokers (−2.5%; *P*-interaction = 0.058). The decreased rates for HPV-unrelated sites were more prominent among those ≥60 years (−11.0%) compared with those <60 years (+16.8%; *P*-interaction = 0.006), among smokers (−9.7%) compared with nonsmokers (+8.4%; *P*-interaction = 0.055), and among those with an alcohol abuse history (−20.4%) compared with those without a history (+5.8%; *P*-interaction = 0.009).

Conclusions: The observed increasing HPV-related cancer rates are most evident among nonsmokers, whereas the decreasing HPV-unrelated cancer rates are least evident among younger individuals, nonsmokers, and those without an alcohol abuse history.

Impact: Continued vigilance for oropharyngeal and oral cavity cancer is warranted, including among those without traditional risk factors such as smoking and alcohol abuse. *Cancer Epidemiol Biomarkers Prev; 24(6); 978–84. ©2015 AACR.*

Introduction

Cancers of the oropharynx and oral cavity are estimated to be diagnosed in 42,440 individuals and cause 8,390 deaths in the United States in 2014 (1). The incidence of oral cavity cancers has significantly declined in the past 3 to 4 decades in the United States and other developed countries, consistent with declines in the major risk factors—tobacco and alcohol use (1–5). Tobacco and alcohol are also strongly associated with oropharyngeal cancer risk (6, 7). Yet, the incidence of oropharyngeal cancers has increased dramatically during the same calendar periods in the United States and elsewhere (8–15). This rapid increase in oropharyngeal cancer incidence has now been attributed to rising incidence of human papillomavirus (HPV)–positive oropharyngeal cancers (8, 10, 13, 16–21). It is believed that changes in sexual behaviors through the 1960s have led to increased oral HPV exposure, and consequently increased HPV-positive oropharyngeal cancer incidence (17, 18, 22–24). Thus, HPV infection has emerged as the major risk factor for oropharyngeal cancers, accounting for approximately 70% of contemporary oropharyngeal cancers in the United States (10, 21, 25).

Given that HPV-positive oropharyngeal cancer incidence has increased during an era of declining smoking prevalence, HPV-positive oropharyngeal cancer has come to be characterized as an epidemic among nonsmokers/nondrinkers (26–28). In parallel, several case–series and case–control studies have shown that patients with HPV-positive oropharyngeal cancers are less likely to have the traditional head and neck cancer risk factors (i.e., smoking and alcohol use; refs. 10, 16, 17, 29–37). However, whether the rise in oropharyngeal cancer incidence in the United States has indeed predominantly occurred among nonsmokers/nondrinkers is not known. Most prior studies of time trends in incidence rates have been conducted through cancer registries, which lack information on tobacco/alcohol use. On the other hand, hospital-based, single-institution studies lack denominator information to allow the estimation of population-based incidence rates.

In the current study, we analyzed data from a large integrated healthcare system—Kaiser Permanente Northern California (KPNC)—to investigate trends in incidence rates for oral cavity cancers and oropharyngeal cancers during 1995 to 2010. More importantly, we utilized participant electronic medical records to

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doi: 10.1158/1055-9965.EPI-14-1416

separately investigate incidence trends stratified by cigarette smoking and alcohol abuse. In addition, we investigated secular changes in demographic and clinical characteristics of patients with oropharyngeal cancers over 15 years.

Materials and Methods

Study design, setting, and participants

We conducted a cohort study of approximately 2 million adults ages 20 to 89 that were health plan members of KPNC during 1995 to 2010. KPNC is a large integrated healthcare delivery system providing comprehensive medical care to more than 3 million members, representing roughly 30% of insured Northern Californians (38). KPNC members are similar to the California statewide population with respect to age, sex, and race/ethnicity (38). All KPNC health plan members have access to primary care and comprehensive specialty services, including otolaryngology, radiation oncology, and oncology. The Institutional Review Board at KPNC approved the study, providing a waiver of informed consent.

Outcome measurement

We identified incident cancers among our study cohort by record linkage with the KPNC cancer registry, a contributing site to the Surveillance, Epidemiology, and End Results (SEER) program. Cancer case ascertainment is considered highly valid, as reporting of cancers to the California Cancer Registry and the National Cancer Institute SEER program is mandated under state law. The primary outcomes of interest were the cancer groups of HPV-related and HPV-unrelated cancers, based on anatomic site. HPV-related oropharyngeal cancers, as defined by Chaturvedi and colleagues (17), included the following anatomic sites (ICD-O-3 site codes): base of tongue (C01.9), lingual tonsil (C02.4), palatine tonsil (C09.0-09.9), oropharynx (C10.0-10.9), and Waldeyer's ring (C14.2). HPV-unrelated cancers included the following sites: tongue excluding base of tongue and lingual tonsil (C02.0-C02.3, C02.5-C02.9), gum (C03.0-C03.9), floor of mouth (C04.0-C04.9), palate (C05.0-C05.9), and other and unspecified mouth (C06.0-C06.9). All cases were limited to squamous cell histology (ICD-0-3 histology codes: 8050 to 8076, 8078, 8083, 8084, and 8094). In addition, we analyzed more common subsites within groups, including base of tongue, tonsil, and oropharynx sites for HPV-related cancers and oral tongue and mouth sites for HPV-unrelated cancers.

Exposure measurement

All information for the study was collected on adult KPNC members from historical electronic clinical and administrative databases. KPNC implemented an extensive and integrated electronic medical record (EMR) system in 2004, but has maintained electronic data on diagnoses, procedures, prescriptions, and laboratory results since 1995 or earlier.

For all study years, 1995–2010, we computed the mid-year KPNC population size for strata defined by age (per year) and sex, using demographic and membership databases. These data were used as the denominator for calculation of oropharyngeal and oral cavity incidence rates. For years 2007–2010 only, we collected additional information for the entire population on a history of smoking and alcohol abuse in the prior 2 years. We limited to more recent years since a primary goal of the study was to document changes in these risk factors over time, and we wanted to ensure similar ascertainment of smoking and alcohol abuse after implementation of the EMR in 2004. Alcohol abuse was defined by any clinical documentation of alcohol abuse or alcohol dependence based on International Classification of Disease codes, version 9 (ICD-9) codes 219, 303, and 305. Smoking was defined by any clinical documentation of tobacco use or dependence based on ICD-9 codes 305.1, V15, V65, 649, and KPNC internal social history codes. For smoking and alcohol abuse, the risk factor was considered present if documented in the medical record, and not present otherwise. Thus, there was no missing information for these variables in the analysis.

In addition, we collected race/ethnicity for cancer cases only, since this information is routinely collected for the KPNC Cancer registry, but not comprehensively for the general KPNC membership. Finally, for cancer cases only, we linked member home addresses to 2000 census-block characteristics to define census-based measures of lower education (i.e., $\geq$25% in census tract <high school diploma) and lower income (i.e., $\geq$20% in census tract below poverty line).

Statistical analysis

We compared demographics between those diagnosed with cancers at HPV-related sites and HPV-unrelated sites. A *P* value was computed based on the χ^2 test for categorical variables (sex, race/ethnicity, diagnosis year, and census-based education, and income) and the *t* test for continuous variables (age). We also evaluated changes in these same factors over time for cases for years 1995 to 2010. In addition, we evaluated changes in smoking and alcohol abuse for cases for years 2007 to 2010. A *P*-trend was computed based on using linear regression for age (as the outcome) or logistic regression for the remaining variables, with calendar year as the predictor. Poisson Regression models were used to evaluate calendar trends in cancer incidence rates adjusting for other factors. Models for HPV-related and HPV-unrelated cancers were fit for all years (1995–2010), with calendar year, age, and sex as the predictors. Additional models were evaluated for the years 2007 to 2010 with the inclusion of smoking and alcohol abuse. Finally, we investigated trends in oropharyngeal and oral cavity cancer incidence stratified by smoking and alcohol abuse through models that included interaction terms for each of these factors and calendar year.

Results

Between 1995 and 2010, we observed a total of 2,727 incident oropharyngeal and oral cavity cases among the entire adult KPNC population, which contributed a total of 34.2 million person-years. HPV status was determined based on anatomic site. In order to validate the classification of HPV-related sites, we performed a manual chart review of all HPV-related cancers diagnosed in 2010, since HPV testing was more routine starting this year. Of 75 HPV-related cancers, 83% tested positive for HPV by P16 or *in situ* hybridization. A total of 1,383 cancers (50.7%) occurred at HPV-related sites, corresponding with an incidence rate of 4.0 per 100,000 person-years, and 1,344 cancers (49.3%) occurred at HPV-unrelated sites, corresponding with an incidence rate of 3.8 per 100,000 person-years. Cancers from HPV-related sites were diagnosed at a younger age compared with HPV-unrelated sites (60.8 vs. 63.8 years; $P < 0.001$) and had a distinct male predominance (77.4% vs. 54.9%; $P < 0.001$; Table 1).

Table 1. Characteristics of patients with oropharyngeal cancer from KPNC, 1995–2010

Characteristic	Type of oropharyngeal cancer		
	HPV-related sites[a]	HPV-unrelated sites[a]	*P*[d]
Total cases	1,383	1,344	
Mean age at diagnosis, years (SD)	60.8 (10.7)	63.8 (12.8)	<0.001
Male sex, %	77.4	54.9	<0.001
Race/ethnicity, %			<0.001
White	83.5	79.0	
Black	5.9	4.5	
Asian/Pacific Islander	4.3	9.0	
Hispanic	6.0	7.1	
Other/unknown	0.3	0.4	
Cancer diagnosis year, %			<0.001
1995–1998	15.5	24.3	
1999–2002	20.7	24.6	
2003–2006	30.7	24.5	
2007–2010	33.2	26.6	
Census-based education[b], %			
Lower education	17.9	18.3	0.80
Higher education	82.1	81.7	
Census-based income[c], %			
Lower income	4.9	6.1	0.18
Higher income	95.1	93.9	
Prior smoking[e], %			
No	43.5	46.7	0.71
Yes	54.7	53.3	
Prior alcohol abuse[e], %			
No	74.5	74.0	0.87
Yes	25.5	26.0	

[a]Defined by histologic site of cancer as described by Chaturvedi et al. (17).
[b]Lower education census-tract defined as ≥25% population with less than a high school education.
[c]Lower income census-tract defined as ≥20% population with household income below poverty levels.
[d]*P* value based on χ^2 for categorical variables and *t* test for continuous variables.
[e]Based on data for 2007–2010, corresponding with $N = 459$ HPV-related and $N = 358$ HPV-unrelated sites.

HPV-related cancers were also more commonly diagnosed in later calendar periods than HPV-unrelated ($P < 0.001$). No differences were observed comparing HPV-related and HPV-unrelated cancers with respect to census-based education ($P = 0.80$) or income ($P = 0.18$).

Next, separately for HPV-related and HPV-unrelated cancer sites, we examined changes over time in selected demographic and clinical characteristics (Table 2). Among HPV-related cancers diagnosed between 1995 and 2010, the percentage that were men increased from 65.4% in 1995 to 80.2% in 2010 ($P < 0.001$), whereas age ($P = 0.40$), race/ethnicity ($P = 0.88$), education census-tract ($P = 0.82$), and income census-tract ($P = 0.97$) of cases did not change over time. For the period 2007–2010, the percentage of HPV-related cases with a smoking history decreased from 55.2% in 2007 to 45.2% in 2010 ($P = 0.046$), whereas the percentage with an alcohol abuse history did not change ($P = 0.98$). Among HPV-unrelated cancers, the percentage who were of white race decreased (90% to 84% in 1995–2010; $P = 0.033$), and there was a trend for a decline in smoking (61% to 48% in 2007–2010; $P = 0.070$) and alcohol abuse (31% to 20% in 2007–2010; $P = 0.10$).

The incidence of HPV-related cancers significantly increased by 3.8% per year during 1995–2010 ($P < 0.001$), with adjustment for age and sex (Figure 1). In Table 3, we present rate ratios (RRs) for HPV-related and HPV-unrelated sites for the years 2007–2010, with adjustment for calendar year, age, sex, smoking, and alcohol abuse. For HPV-related sites, there was a nonsignificant increase in incidence rates of 5.0% per year ($P = 0.25$), similar in magnitude to unadjusted calendar trends for entire period of 1995–2010. Significant risk factors for HPV-related cancers included older age (RR per 10 years = 1.5; $P < 0.001$), male sex (RR = 5.3; $P < 0.001$), smoking (RR = 2.1; $P < 0.001$), and alcohol abuse (RR = 2.2; $P < 0.001$). Similar findings for risk factors were noted for individual HPV-related anatomic sites (i.e., base of tongue, tonsil, and oropharynx), except for an attenuated association of male sex for oropharynx sites (RR = 2.0; $P = 0.06$), and a stronger association with smoking (RR = 3.8; $P < 0.001$).

Table 2. Change in characteristics of patients with oropharyngeal cancer from KPNC between 1995 and 2010

Characteristic	Calendar year of cancer diagnosis						
	1995	1998	2001	2004	2007	2010	*P*-trend[a]
A. HPV-related sites[b]							
Total cases	52	55	71	114	96	126	
Mean age, years	62.8	59.4	60.8	60.6	60.0	60.9	0.40
Male sex, %	65.4	67.3	69.0	83.3	81.3	80.2	**<0.001**
White race, %	90.4	70.9	91.6	86.8	82.3	84.1	0.88
Prior smoking, %					55.2	45.2	**0.046**
Prior alcohol abuse, %					22.9	24.6	0.98
Lower education census-tract, %	17.5	24.5	13.0	15.0	24.0	18.2	0.82
Lower income census-tract, %	2.5	5.7	4.4	2.8	4.2	3.3	0.97
B. HPV-unrelated sites[b]							
Total cases	77	82	91	82	95	95	
Mean age, years	65.0	63.4	66.1	65.0	65.0	62.2	0.71
Male sex, %	55.8	57.3	53.9	61.0	52.6	50.5	0.23
White race, %	81.8	84.2	82.4	78.1	77.9	72.6	**0.033**
Prior smoking, %					61.1	48.4	**0.070**
Prior alcohol abuse, %					30.5	20.0	**0.10**
Lower education census-tract[c], %	17.4	26.3	18.8	14.6	14.7	16.5	0.15
Lower income census-tract[d], %	8.7	9.2	3.5	8.5	4.2	2.2	0.13

NOTE: Findings in bold are statistically significant.
[a]*P*-trend based on linear regression for age and logistic regression for remaining variables, with calendar year as the predictor.
[b]Defined by histologic site of cancer as described by Chaturvedi et al. (17).
[c]Lower education census-tract defined as ≥25% population with less than a high school education.
[d]Lower income census-tract defined as ≥20% population with household income below poverty levels.

Table 3. Selected risk factors among patients with oropharygneal cancer from KPNC, 2007–2010

	A. HPV-related oropharyngeal cancer sites[a]							
	Any HPV-related		Tongue (HPV$^+$)		Tonsil		Oropharynx	
	RR[b] (95% CI)	*P*	RR[b] (95% CI)	*P*	RR[b] (95% CI)	*P*	RR[b] (95% CI)	*P*
Year (per 1 year)	1.05 (0.97–1.14)	0.25	1.03 (0.92–1.17)	0.593	1.07 (0.95–1.20)	0.285	1.04 (0.76–1.41)	0.816
Age (per 10 years)	1.53 (1.44–1.62)	<0.001	1.62 (1.49–1.77)	<0.001	1.43 (1.31–1.55)	<0.001	1.71 (1.36–2.14)	<0.001
Male sex	5.34 (4.18–6.83)	<0.001	5.90 (4.06–8.56)	<0.001	5.90 (4.07–8.56)	<0.001	2.03 (0.98–4.20)	0.056
Smoking[c]	2.12 (1.73–2.58)	<0.001	1.95 (1.46–2.62)	<0.001	2.10 (1.57–2.82)	<0.001	3.84 (1.74–8.50)	<0.001
Alcohol abuse[c]	2.20 (1.76–2.75)	<0.001	1.90 (1.35–2.68)	<0.001	2.43 (1.76–3.36)	<0.001	2.70 (1.26–5.82)	0.011

	B. HPV-unrelated oropharyngeal cancer sites[a]					
	Any HPV-unrelated		Tongue (HPV$^-$)		Mouth	
	RR[b] (95% CI)	*P*	RR[b] (95% CI)	*P*	RR[b] (95% CI)	*P*
Year (per 1 year)	0.98 (0.90–1.08)	0.750	1.04 (0.91–1.18)	0.581	0.93 (0.81–1.06)	0.279
Age (per 10 years)	1.71 (1.60–1.83)	<0.001	1.58 (1.45–1.73)	<0.001	1.91 (1.72–2.13)	<0.001
Male sex	1.20 (0.97–1.47)	0.092	1.16 (0.88–1.54)	0.301	1.23 (0.90–1.68)	0.186
Smoking[c]	2.08 (1.66–2.61)	<0.001	1.58 (1.17–2.15)	0.003	2.98 (2.11–4.22)	<0.001
Alcohol abuse[c]	2.42 (1.88–3.12)	<0.001	1.90 (1.31–2.77)	<0.001	3.08 (2.18–4.37)	<0.001

[a]Defined by histologic site of cancer as described by Chaturvedi et al. (17).
[b]Rate ratios from multivariable Poisson Regression model adjusted for all variables in table.
[c]Corresponds to smoking or alcohol abuse diagnosis in prior 2 years.

The incidence of cancer at HPV-unrelated sites significantly decreased by 2.4% per year during 1995–2010 ($P < 0.001$), with adjustment for age and sex (Fig. 1). For HPV-unrelated sites, incidence rates were stable during 2007–2010, with a nonsignificant decline of 1.5% per year ($P = 0.75$), again similar in magnitude to unadjusted calendar trends for entire period of 1995–2010. Significant risk factors for HPV-unrelated sites included older age (RR per 10 years = 1.7; $P < 0.001$), smoking (RR = 2.1; $P < 0.001$), and alcohol abuse (RR = 2.4; $P < 0.001$). For HPV-unrelated cancers, the RR for male sex was only 1.2 ($P = 0.09$). Similar findings for risk factors were noted for individual HPV-unrelated anatomic sites (i.e., oral tongue and mouth), except for stronger associations for smoking (RR = 3.0; $P < 0.001$) and alcohol abuse (RR = 3.1; $P < 0.001$) for mouth cancers.

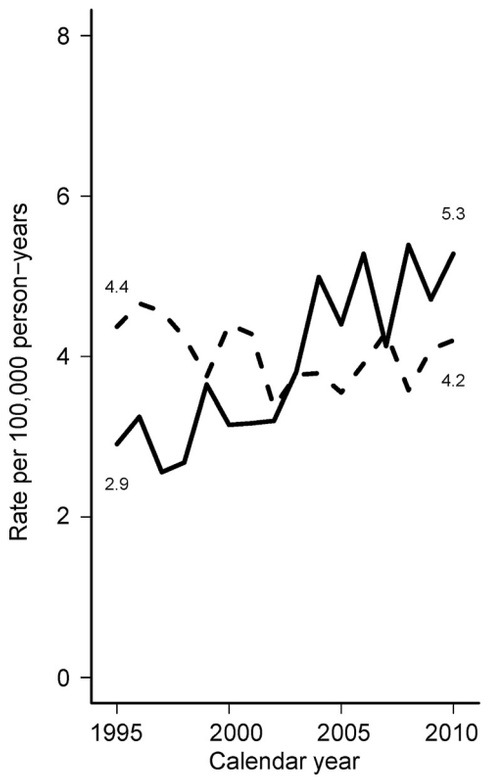

Figure 1.
Incidence rates over time for patients with oropharyngeal carcinoma. Incidence rates per 100,000 person-years are presented for years 1995–2010 for oropharyngeal carcinoma, categorized as any, HPV-related (solid line), and HPV-unrelated (dashed line), defined by histologic site of cancer as described by Chaturvedi et al. (17). The corresponding age- and sex-adjusted calendar trends were +3.8%/year ($P < 0.001$) for HPV-related sites, and −2.4%/year ($P < 0.001$) for HPV-unrelated sites. Numbers on plots correspond with incidence rates (per 100,000 person-years) for years 1995 and 2010.

We observed notable heterogeneity in incidence trends during 2007–2010 for both HPV-related and HPV-unrelated sites across subgroups defined by smoking, age, and alcohol abuse. As shown in Table 4A, for HPV-related sites, rising incidence was observed exclusively among nonsmokers, whereas incidence rates did not change significantly among smokers. Notably, among nonsmokers, incidence rates for HPV-related sites nearly doubled from 2007 (2.4 per 100,000 person-years) to 2010 (3.9 per 100,000 person-years). Table 4B shows that for HPV-unrelated sites, trends were heterogeneous by age, smoking, and alcohol abuse. For HPV-unrelated sites, those aged 60 years or older had an 11.0% decline ($P = 0.054$) in incidence rates per year compared with a 16.8% increase ($P = 0.047$) for those under 60 (P-interaction = 0.006). In absolute terms, the incidence rate for those under 60 increased from 1.7 cases per 100,000 person-years in 2007 to 2.4 cases per 100,000 person-years in 2010. Likewise, for those over the age of 60, the absolute incidence rate decreased from 11.7 to 8.9 cases per 100,000 person-years. For HPV-unrelated sites, we found a 9.7% decline ($P = 0.12$) in incidence rates per year for smokers compared with an 8.4% increase ($P = 0.24$) for those without a smoking history (P-interaction = 0.055). Those with an alcohol abuse history had a 20.5% decline ($P = 0.016$) in incidence rates per year compared with a nonsignificant 5.8% increase (P = 0.30) for those without an alcohol abuse history (P-interaction = 0.009). The decreasing incidence rates for HPV-unrelated sites with an alcohol abuse history were dramatic, from 17.6 per 100,000 person-years in 2007 to 8.2 in 2010. Finally, no difference in calendar trends for HPV-unrelated sites was observed for strata defined by sex (P-interaction = 0.68). Finally, in Fig. 2, we present incidence rates stratified by both prior

Table 4. Adjusted calendar trends for patients with oropharyngeal cancer overall and by prior history of smoking and alcohol abuse, 2007–2010

Smoking and alcohol abuse strata[a], by cancer group	RR, per year[b] (95% CI)	*P*	*P*-interaction
A. HPV-related sites[c]			
Age <60 years	1.05 (0.93–1.19)	0.41	0.98
Age ≥60 years	1.05 (0.94–1.18)	0.37	
Men	1.05 (0.96–1.15)	0.32	0.89
Women	1.06 (0.87–1.30)	0.54	
Smoking history	0.98 (0.87–1.09)	0.66	
No smoking history	1.14 (1.01–1.29)	0.030	0.058
Alcohol abuse	0.98 (0.83–1.16)	0.82	
No alcohol abuse	1.07 (0.98–1.18)	0.14	0.35
B. HPV-unrelated sites[c]			
Age <60 years	1.17 (1.00–1.36)	0.047	0.006
Age ≥60 years	0.89 (0.79–1.00)	0.054	
Men	1.00 (0.88–1.14)	0.96	0.68
Women	0.96 (0.84–1.10)	0.60	
Smoking history	0.90 (0.79–1.03)	0.12	
No smoking history	1.08 (0.95–1.24)	0.24	0.055
Alcohol abuse	0.80 (0.66–0.96)	0.016	
No alcohol abuse	1.06 (0.95–1.18)	0.30	0.009

[a]Corresponds to smoking or alcohol abuse diagnosis in prior 2 years.
[b]Rate ratios for calendar year from multivariable Poisson Regression model with terms for year, age, sex, alcohol, and smoking. For smoking-stratified models, we included a smoking/year interaction term, and for alcohol-stratified models, we included an alcohol/year interaction term.
[c]Defined by histologic site of cancer as described by Chaturvedi et al. (17).

smoking and alcohol abuse history. For nonsmokers (Fig. 2A and B) there were increasing trends in incidence rates for HPV-related sites. For those with both smoking and alcohol abuse history (Fig. 2D), there was a large decrease in HPV-unrelated incidence rates.

Discussion

Our data from a large, diverse cohort of patients from KPNC uniquely inform secular trends for the development of oropharyngeal cancer in relation to the key risk factors of smoking history and alcohol abuse. Our three principal findings were the following: (i) incidence rates of HPV-related cancer sites significantly increased during 1995–2010, and this increase was most prominent among nonsmokers; (ii) incidence rates of HPV-unrelated cancers declined during 1995–2010, most prominently for those older than age 60 and those with a history of alcohol abuse; and (iii) the patient profile for oropharyngeal cancer in recent years was increasingly among men and nonsmokers.

Our observed rise in the overall incidence rate for HPV-related oropharyngeal cancer was consistent with other reports in the recent literature (8, 10, 12, 13, 16, 17, 21). The increased incidence for oropharyngeal cancer at HPV-related sites has been attributed to increased prevalence of HPV infection, whereas the decreased incidence at HPV-unrelated sites has been attributed to decreased smoking (2, 10). Several studies show that sexual behaviors are strongly associated with an increased risk of developing an HPV-positive oropharyngeal cancer (18, 23–25, 31–34, 36). Presumably, changes in sexual behaviors in recent birth cohorts/calendar periods have led to increased oral HPV exposure and subsequent risk of HPV-positive oropharyngeal cancer (23, 24, 32–34, 36).

HPV-positive oropharyngeal cancer has come to be characterized as a disease of never-smokers and nondrinkers. However, this evidence comes from case–series and case–control series (16, 19, 30, 32), and none have specifically looked at incidence rates stratified by these behavioral factors. Our study provides further evidence that the rising HPV-related oropharyngeal cancer incidence in the KPNC cohort was most apparent among nonsmokers. In addition, our data highlight the significant contribution of smoking as an important risk factor even among HPV-related oropharyngeal cancers. We found that the incidence rate for the development of HPV-related oropharyngeal cancer among smokers was more than double the rate for nonsmokers and was unchanging over the study period. Thus, HPV-related cancers remain a significant burden for smokers, yet the observed rise in these cancers is predominantly among nonsmokers.

The increase in HPV-unrelated oropharyngeal cancer seen among the young, despite overall declines, is also consistent with recent literature of oral tongue cancers (13–15, 29, 39, 40). At least one report identified an increase in oral tongue cancer incidence in young, white, nonsmoking, nondrinking women, with tumors negative for HPV DNA with no clear cause yet identified (13). Possible explanations include misclassification of base of tongue as oral tongue, other oncogenic viral infections, and other environmental exposures.

Our data add to the current literature describing the changing profile of patients newly diagnosed with oropharyngeal cancer in the U.S. general population, generalized as male, middle-aged, white, nonsmoking, and nondrinking. This has significant prognostic implications in that HPV-related oropharyngeal cancer is associated with improved survival rates compared with HPV-unrelated oropharyngeal cancer (10, 16, 18, 35, 37, 41–47). It is significant to note that oropharyngeal cancer is close to becoming the most common of all head and neck cancers due to

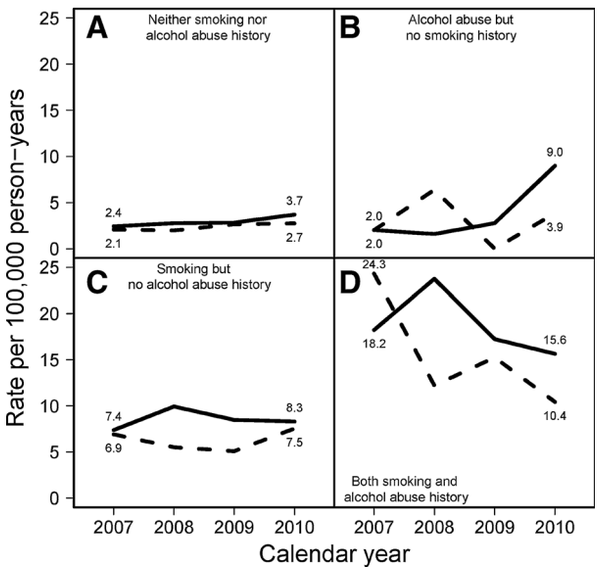

Figure 2.
Incidence rates over time for patients with oropharyngeal carcinoma by smoking and alcohol abuse history, 2007–2010. Incidence rates per 100,000 person-years are presented for years 2007–2010 for oropharyngeal carcinoma, categorized as HPV-related (solid line) and HPV-unrelated (dashed line), defined by histologic site of cancer as described by Chaturvedi et al. (17). Incidence rates are shown stratified by prior smoking and alcohol abuse history: neither (A); only alcohol abuse (B); only smoking (C); or both (D). Numbers on plots correspond with incidence rates (per 100,000 person-years) for years 2007 and 2010.

decreasing rates of oral cavity and larynx cancer that has resulted from lower rates of smoking in the U.S. population (1, 2, 7, 8, 17, 48).

Potential limitations of this study are that smoking and alcohol abuse data are from the clinical record and therefore did not include information on either duration or intensity of smoking and alcohol use. In addition, misclassification is possible, since the absence of a smoking or alcohol abuse diagnosis was not routinely recorded in the medical record. However, the misclassification would likely be nondifferential with respect to calendar time, and the observed strong independent associations of these factors with cancer provide evidence against significant bias. An additional limitation of the smoking and alcohol abuse data was the availability only for years 2007–2010. Nonetheless, the trends observed in 2007–2010 were consistent in magnitude with trends observed over the entire study period 1995–2010. A final limitation was the designation of HPV-related and HPV-unrelated sites based upon anatomic location alone. However, previous studies have indicated an acceptable, approximately 70% concordance between HPV results based on anatomic site and direct measurement of HPV infection (17). Our validation chart review, although based on small numbers, indicated >80% of HPV-related cancers in 2010 tested positive for HPV.

In summary, our data from a large population-based cohort support the observation of rising HPV-related and declining HPV-unrelated cancer incidence rates, and, to our knowledge, this is the first study to describe incidence trends by smoking and alcohol abuse status. The observed changing epidemiology of HPV-related oropharyngeal cancer also has important clinical implications, given the improved survival potential for HPV-positive oropharyngeal cancer patients on current treatments and the possibility for de-intensified therapy in the future. There are public health implications as well, such as the opportunity for primary prevention through prophylactic vaccination for young boys as well as young girls given that HPV-related cancers are increasingly common in men. Clinicians must remain vigilant in identifying HPV-related oropharyngeal cancers particularly in the typical patient who is younger, and without a smoking or alcohol abuse history, but must not overlook those with a smoking history who still account for up to half of HPV-related cases in the current era.

Disclosure of Potential Conflicts of Interest

M.J. Silverberg reports receiving a commercial research grant from Pfizer and Merck. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: J.A. Katzel
Development of methodology: J.A. Katzel, M. Merchant
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.A. Katzel, M. Merchant
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.A. Katzel, M. Merchant, A.K. Chaturvedi, M.J. Silverberg
Writing, review, and/or revision of the manuscript: J.A. Katzel, M. Merchant, A.K. Chaturvedi, M.J. Silverberg
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.A. Katzel, M. Merchant
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Acknowledgments

The authors thank Dr. A. Dimitrios Colevas, Division of Oncology, Stanford University Medical Center, for critical review of a draft of the article.

Grant Support

J.A. Katzel was awarded a Kaiser Permanente Community Benefit research grant. A.K. Chaturvedi is employed by the NIH.

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Received December 23, 2014; revised March 16, 2015; accepted March 26, 2015; published OnlineFirst May 8, 2015.

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