Research Article

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A Sex-Specific Association between a 15q25 Variant and Upper Aerodigestive Tract Cancers

Dan Chen[1], Therese Truong[1], Valerie Gaborieau[1], Graham Byrnes[1], Amelie Chabrier[1], Shu-chun Chuang[1], Andrew F. Olshan[2,3], Mark C. Weissler[4], Jingchun Luo[5], Marjorie Romkes[6], Shama Buch[6], Tomoko Nukui[6], Silvia Franceschi[1], Rolando Herrero[7], Renato Talamini[8], Karl T. Kelsey[9], Brock Christensen[9], Michael D. McClean[10], Martin Lacko[11], Johannes J. Manni[11], Wilbert H. M. Peters[12], Jan Lubiński[13], Joanna Trubicka[13], Marcin Lener[13], Joshua E. Muscat[14], Philip Lazarus[14], Qingyi Wei[15], Erich M. Sturgis[15], Zuo-Feng Zhang[16], Shen-Chih Chang[16], Renyi Wang[16], Stephen M. Schwartz[17], Chu Chen[17], Simone Benhamou[18,19], Pagona Lagiou[20], Ivana Holcátová[21], Lorenzo Richiardi[22], Kristina Kjaerheim[23], Antonio Agudo[24], Xavier Castellsagué[24,25], Tatiana V. Macfarlane[26], Luigi Barzan[27], Cristina Canova[28,29], Nalin S. Thakker[30], David I. Conway[31], Ariana Znaor[32], Claire M. Healy[33], Wolfgang Ahrens[34], David Zaridze[35], Neonila Szeszenia-Dabrowska[36], Jolanta Lissowska[37], Eleonora Fabianova[38], Alexandru Bucur[39], Vladimir Bencko[21], Lenka Foretova[40], Vladimir Janout[41], Maria Paula Curado[1], Sergio Koifman[42], Ana Menezes[43], Victor Wünsch-Filho[44], José Eluf-Neto[44], Leticia Fernandez[45], Stefania Boccia[46,47], Mia Hashibe[1,48], Richard B. Hayes[49], Paolo Boffetta[1,50,51], Paul Brennan[1], and James D. McKay[1]

Abstract

Background: Sequence variants located at 15q25 have been associated with lung cancer and propensity to smoke. We recently reported an association between rs16969968 and risk of upper aerodigestive tract (UADT) cancers (oral cavity, oropharynx, hypopharynx, larynx, and esophagus) in women (OR = 1.24, $P = 0.003$) with little effect in men (OR = 1.04, $P = 0.35$).

Methods: In a coordinated genotyping study within the International Head and Neck Cancer Epidemiology (INHANCE) consortium, we have sought to replicate these findings in an additional 4,604 cases and 6,239 controls from 10 independent UADT cancer case–control studies.

Results: rs16969968 was again associated with UADT cancers in women (OR = 1.21, 95% CI = 1.08–1.36, $P = 0.001$) and a similar lack of observed effect in men [OR = 1.02, 95% CI = 0.95–1.09, $P = 0.66$; *P*-heterogeneity (P_{het}) = 0.01]. In a pooled analysis of the original and current studies, totaling 8,572 UADT cancer cases and 11,558 controls, the association was observed among females (OR = 1.22, 95% CI = 1.12–1.34, $P = 7 \times 10^{-6}$) but not males (OR = 1.02, 95% CI = 0.97–1.08, $P = 0.35$; $P_{het} = 6 \times 10^{-4}$). There was little evidence for a sex difference in the association between this variant and cigarettes smoked per day, with male and female rs16969968 variant carriers smoking approximately the same amount more in the 11,991 ever smokers in the pooled analysis of the 14 studies ($P_{het} = 0.86$).

Conclusions: This study has confirmed a sex difference in the association between the 15q25 variant rs16969968 and UADT cancers.

Impact: Further research is warranted to elucidate the mechanisms underlying these observations. *Cancer Epidemiol Biomarkers Prev; 20(4); 658–64. ©2011 AACR.*

Authors' Affiliations: [1]International Agency for Research on Cancer (IARC), Lyon, France; [2]Gillings School of Global Public Health; [3]School of Medicine; [4]Otolaryngology/Head and Neck Surgery; and [5]Lineberger Comprehensive Cancer Site, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; [6]University of Pittsburgh, Pittsburgh, Pennsylvania; [7]Instituto de Investigación Epidemiológica, San José, Costa Rica; [8]National Cancer Institute, IRCSS, Aviano, Italy; [9]Brown University, Providence, Rhode Island; [10]Boston University School of Public Health, Boston, Massachusetts; [11]Department of Otorhinolaryngology and Head and Neck Surgery, Maastricht University Medical Site, Maastricht; and [12]Department of Gastroenterology, Radboud University Nijmegen Medical Site, Nijmegen, the Netherlands; [13]Pomeranian Medical University, Department of Genetics and Pathomorphology, International Hereditary Cancer Site, Szczecin, Poland; [14]Penn State College of Medicine, Hershey, Pennsylvania; [15]University of Texas MD Anderson Cancer Site, Houston, Texas; [16]University of California, Los Angeles, School of Public Health, Los Angeles, California; [17]Fred Hutchinson Cancer Research Site, Seattle, Washington; [18]INSERM U946, Paris; [19]CNRS UMR8200, Gustave Roussy Institute, Villejuif, France; [20]University of Athens School of Medicine, Athens, Greece; [21]Institute of Hygiene and Epidemiology,1st Faculty of Medicine, Charles University in Prague, Czech Republic; [22]Unit of Cancer Epidemiology, University of Turin, Turin, Italy; [23]Cancer Registry of Norway, Oslo, Norway; [24]Institut Català d'Oncologia (ICO), Barcelona; and [25]Consortium for Biomedical Research in Epidemiology and Public Health (CIBER Epidemiologia y Salud Publica - CIBERESP), Spain; [26]School of Medicine and Dentistry, University of Aberdeen, Aberdeen, United Kingdom; [27]General Hospital of Pordenone, Pordenone; [28]Department of Environmental Medicine and Public Health, University of Padova, Padova, Italy; [29]MRC-HPA Centre for Environment and Health, Department of Respiratory Epidemiology and Public Health, D, Imperial College School of Medicine (NHLI), London and; [30]University of Manchester, School of Dentistry, Manchester, United Kingdom; [31]University of Glasgow Dental School, Glasgow, Scotland; [32]Croatian National Cancer Registry, Croatian National Institute of Public

Introduction

Exposure to alcohol and tobacco are the major risk factors for upper aerodigestive tract (UADT) cancers (cancers of the oral cavity, oropharynx, hypopharynx, larynx, and esophagus) in Europe and America (1).

Common genetic variants located at chromosome 15q25, a locus that contains 3 genes that encode nicotinic acetylcholine receptor (nAChR) subunits (*CHRNA5*, *CHRNA3*, and *CHRNB4*), have been implicated in the risk of lung cancer, chronic obstructive pulmonary disease (COPD) and peripheral arterial disease (2–5). The same variants are associated with increased propensity to smoke tobacco (4, 6, 7), leading to the hypothesis that this might explain the associations noted with pathologies linked to tobacco exposure (4, 8). Others have suggested that these variants may have additional independent effects (2, 5, 9–11). In a recent study of 3,968 UADT cancer cases and 5,319 controls (10), we observed that there was statistically significant association between 15q25 variant rs16969968 and risk of UADT cancers in women (OR = 1.24, 95% CI = 1.08–1.42, $P = 0.003$) but not men [OR = 1.04, 95% CI = 0.96–1.12, $P = 0.35$; P-heterogeneity (P_{het}) = 0.03]. In the present study, we sought to validate these findings in an independent series of 4,604 UADT cancer cases and 6,239 controls from 10 UADT cancer case–control studies participating in the International Head and Neck Cancer Epidemiology (INHANCE) consortium (12).

Materials and Methods

Study subjects

Ten independent case–control studies of UADT cancers from INHANCE consortium (7 were conducted in America and 3 in Europe) participated in our present study. Study designs and population characteristics have been described in more detail previously (12–15) and are briefly described in Table 1 and Supplementary Table S1. All the subjects included in the pooled analysis were of self-reported European ancestry. As previously described (12), all INHANCE studies have extensive information on tumor site and histology, as well as lifestyle characteristics. The majority of hospital-based studies excluded controls with tobacco-related pathologies as a control source (13–15). The exceptions were the Penn State, Rome, MD Anderson, and Pittsburgh studies that did not exclude tobacco-related pathologies specifically. Written informed consent was obtained from all study subjects and studies were approved by the Institutional Review Boards at each study center. Analysis was restricted to squamous cell carcinomas.

Genotyping and quality control

Genotyping of the 15q25 variant, rs16969968, was carried out in 8 genotyping laboratories (Supplementary Table S1) using the TaqMan genotyping platform (rs16969968 Taqman assay primers GAGTGGTAGTGGACCAAAATCTTCT and ACCTCACGGACATCATTTTCCTT probes VIC-MGB-CTGCGCTCAATTC, FAM-MGB-CTGCGCTCGATTC). A common series of 90 standard DNAs were genotyped at each laboratory to ensure the quality and comparability of the genotyping results across the different studies. The overall concordance with the consensus genotype and the genotypes from the 8 laboratories for the standardized DNAs was 99.86%. Genotype success rate was greater than 95.87% across each site and genotype distributions were consistent with that expected by Hardy–Weinberg equilibrium (HWE).

Statistical analysis

The association between rs16969968 and UADT cancer risk was estimated by ORs and 95% CIs per allele (under log-additive model) and genotype derived from multivariate unconditional logistic regression, with age, sex, and study site (or country when appropriate) included in the model as covariates. Heterogeneity of ORs was assessed using the Cochran's Q test. The association between the rs16969968 variant allele and number of cigarettes smoked per day (CPD) was carried out in ever smokers using multivariate linear regression on log-transformed data. Mean values and 95% CIs were calculated in the combined initial and present data sets with adjustment for age, sex, and study site (and case–control status when appropriate). Differential effect of this single nucleotide polymorphism (SNP) on CPD between sexes was evaluated in a linear regression analysis by including a genotype by sex interaction term.

Health, Zagreb, Croatia; [33]Trinity College School of Dental Science, Dublin, Ireland; [34]Bremen Institute for Prevention Research and Social Medicine (BIPS), University of Bremen, Bremen, Germany; [35]Institute of Carcinogenesis, Cancer Research Site, Moscow, Russia; [36]Department of Epidemiology, Institute of Occupational Medicine, Lodz; [37]The M Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland; [38]Regional Authority of Public Health, Banská Bystrica, Slovakia; [39]Institute of Public Health, Bucharest, Romania; [40]Department of Cancer Epidemiology and Genetics, Masaryk Memorial Cancer Institute, Brno; and [41]Palacky University, Olomouc, Czech Republic; [42]Escola Nacional de Suade Publica, Rio de Janeiro; [43]Universidade Federal de Pelotas, Pelotas; and [44]Universidade de Sao Paulo, Sao Paulo, Brazil; [45]Institute of Oncology and Radiobiology, Havana, Cuba; [46]Institute of Hygiene, Università Cattolica del Sacro Cuore; and [47]IRCCS San Raffaele Pisana, Rome, Italy; [48]University of Utah, School of Medicine, Salt Lake City, Utah; [49]NYU Langone Medical Center New York; and [50]The Tisch Cancer Institute, Mount Sinai School of Medicine, New York, New York; and [51]International Prevention Research Institute, Lyon, France

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Corresponding Author: James D. McKay, International Agency for Research on Cancer (IARC), 150 Cours Albert Thomas, 69372 Lyon CEDEX 08, France. Phone: 3347-273-8093; Fax: 3347-273-8388. E-mail: mckay@iarc.fr

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Table 1. Selected demographic characteristics of study subjects

	Combined series				Women				Men			
	Cases		Controls		Cases		Controls		Cases		Controls	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Age group												
<50	1,624	18.95	2,039	17.64	343	17.26	573	17.18	1,281	19.45	1,466	17.83
50 to <60	2,867	33.45	3,838	33.21	571	28.74	1,049	31.45	2,296	34.87	2,789	33.92
60 to <70	2,591	30.23	3,413	29.53	600	30.20	942	28.25	1,991	30.24	2,471	30.05
≥70	1,490	17.38	2,268	19.62	473	23.80	771	23.12	1,017	15.44	1,497	18.21
Cancer site												
Oral cavity	1,968	22.96			605	30.45			1,363	20.70		
Oropharynx	1,930	22.52			398	20.03			1,532	23.26		
Hypopharynx	440	5.13			57	2.87			383	5.82		
Larynx	2,773	32.35			534	26.87			2,239	34.00		
Esophagus	401	4.68			88	4.43			313	4.75		
Others[a]	870	10.15			232	11.68			638	9.69		
Missing	190	2.22			73	3.67			117	1.78		
Smoking status												
Never smokers	1,093	12.75	3,810	32.96	456	22.95	1,605	48.13	637	9.67	2,205	26.82
Former smokers	1,965	22.92	3,501	30.29	428	21.54	712	21.35	1,537	23.34	2,789	33.92
Current smokers	4,562	53.22	2,827	24.46	919	46.25	602	18.05	3,643	55.32	2,225	27.06
Former or current smokers	539	6.29	393	3.40	112	5.64	80	2.40	427	6.48	313	3.81
Missing	413	4.82	1,027	8.89	72	3.62	336	10.07	341	5.18	691	8.40
Alcohol consumption												
Never drinkers	884	10.31	1,953	16.90	486	24.46	995	29.84	398	6.04	958	11.65
Ever drinkers	7,173	83.68	8,282	71.66	1,346	67.74	1,928	57.81	5,827	88.49	6,354	77.27
Missing	515	6.01	1,323	11.45	155	7.80	412	12.35	360	5.47	911	11.08
Total	8,572		11,558		1,987		3,335		6,585		8,223	

[a]Other cancer sites included oral/pharynx cancer, not otherwise specified, or overlapping head and neck cancer.

Results

In the independent series of 4,604 UADT cancer cases and 6,239 controls, the association between rs16969968 and UADT cancers was found in women (OR = 1.21, 95% CI = 1.08–1.36, $P = 0.001$), with little evidence for association in men (OR = 1.02, 95% CI = 0.95–1.09, $P = 0.66$; $P_{het} = 0.01$; Fig. 1). This is consistent with the observation in the initial study (OR = 1.24, 95% CI = 1.08–1.42 for women; OR = 1.04, 95% CI = 0.96–1.12 for men; $P_{het} = 0.03$; ref. 10). To further evaluate this genetic effect, we pooled individual level data from the initial study and the 10 independent studies presented here, making for a total of 8,572 UADT cancer cases and 11,558 controls from 14 studies. We then conducted stratified analysis in both women and men (Fig. 1). In the combined series, rs16969968 was associated with UADT cancers only in females (females: OR = 1.22, 95% CI = 1.12–1.34, $P = 7 \times 10^{-6}$; males: OR = 1.02, 95% CI = 0.97–1.08, $P = 0.35$; $P_{het} = 6 \times 10^{-4}$). In women, the association of rs16969968 with UADT cancer risk was relatively consistent among subgroups stratified by smoking status, alcohol consumption, and age. Significant heterogeneity was noted by UADT cancer subsite ($P_{het} = 0.02$), with the association strongest among female laryngeal cancer (OR = 1.40, 95% CI = 1.21–1.61, $P = 6 \times 10^{-6}$) and absent in female cancers of the oropharynx (OR = 1.00, 95% CI = 0.84–1.18, $P = 0.97$) and hypopharynx (OR = 0.95, 95% CI = 0.63–1.43, $P = 0.80$). Evidence for association was also present in female never smokers (OR = 1.18, 95% CI = 1.00–1.39, $P = 0.05$) and never drinkers (OR = 1.35, 95% CI = 1.14–1.61, $P = 6 \times 10^{-4}$). In contrast, in men there was little evidence for association between rs16969968 and UADT cancers in any stratum.

The rs16969968 variant has been consistently associated with propensity to smoke cigarettes (particularly CPD; refs. 4, 6, 7), we therefore examined whether rs16969968 was associated with CPD among 11,991 ever smokers included in the combined initial and present data sets, as well as in UADT cancer cases and controls separately and among males and females (Table 2). In the combined series, the rs16969968 minor allele was

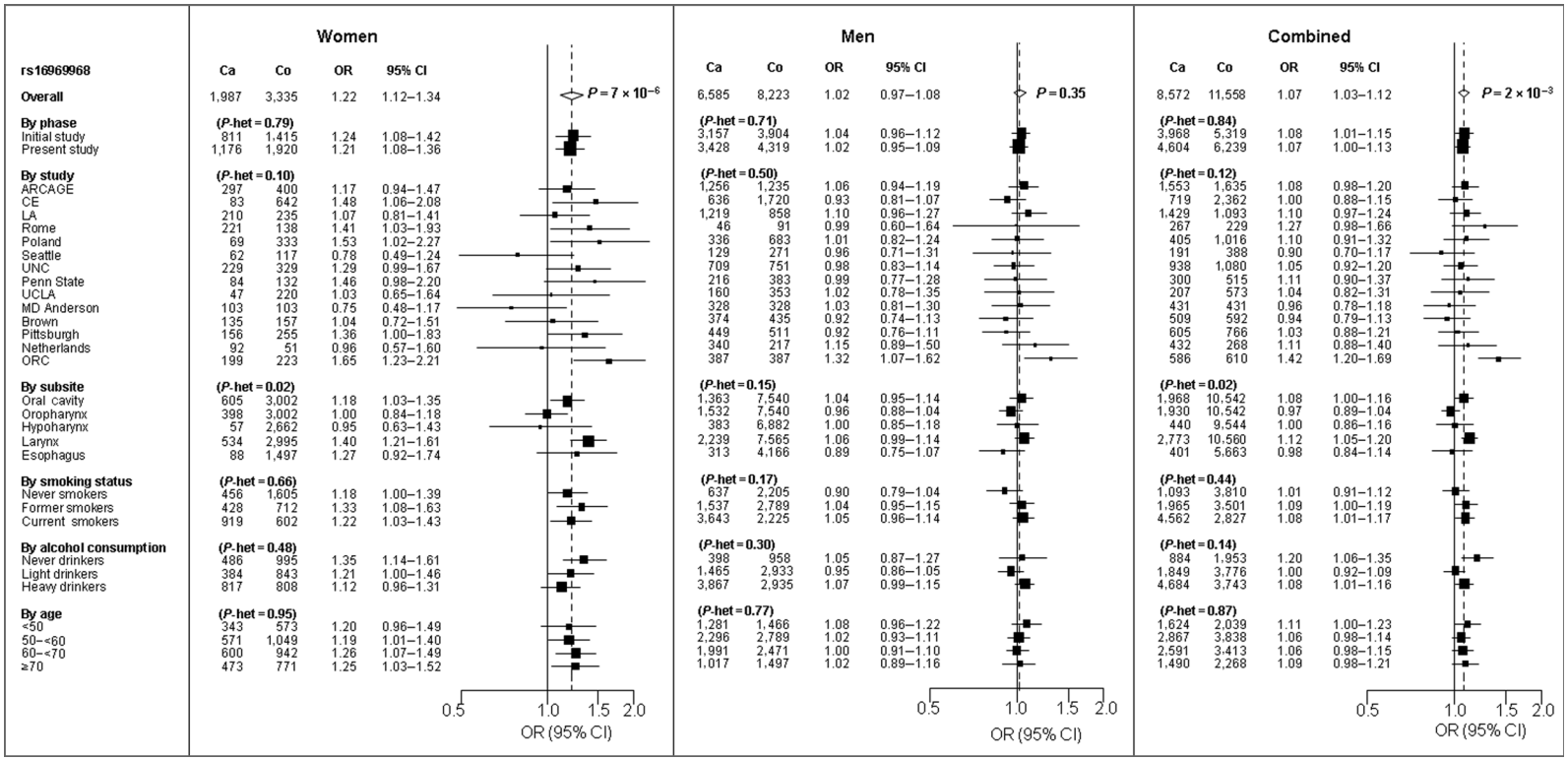

Figure 1. Forest plots representing the association between rs16969968 and UADT cancer risk in women, men, and the combined series, respectively. Unless specified, the ORs and 95% CIs were derived from the log-additive genetic model with adjustment for age, study site, and sex when appropriate. P_{het} was derived from the Cochran's Q test. The overall OR is shown by the dotted vertical line. For each study among drinkers, individuals were defined as light drinkers if they consumed below the median level of ethanol per day; otherwise, they were considered as heavy drinkers.

Table 2. Association between rs16969968 and CPD

Group	Genotype	Cases			Controls			Overall		
		n	Mean[a]	95% CI[a]	*n*	Mean[a]	95% CI[a]	*n*	Mean[a]	95% CI[a]
Combined	GG	2,632	20.83	20.11–21.55	2,636	17.07	16.34–17.80	5,268	18.97	18.46–19.47
	GA	2,725	21.24	20.54–21.94	2,635	17.43	16.70–17.80	5,360	19.33	18.84–19.83
	AA	709	22.24	21.17–23.31	654	19.08	17.94–20.22	1,363	20.69	19.92–21.47
P_{trend}[b]			0.02			2×10^{-5}			1×10^{-6}	
Women	GG	432	18.53	17.08–19.98	500	13.69	12.41–14.97	932	15.97	15.04–16.90
	GA	457	17.39	16.01–18.77	513	14.20	12.97–15.42	970	15.76	14.87–16.65
	AA	130	18.80	16.67–20.93	114	15.36	13.24–17.49	244	17.26	15.78–18.74
P_{trend}[b]			0.89			0.20			0.18	
Men	GG	2,200	23.48	22.73–24.22	2,136	19.80	18.97–20.64	4,336	21.73	21.19–22.27
	GA	2,268	24.20	23.48–24.92	2,122	20.13	19.29–20.97	4,390	22.22	21.69–22.76
	AA	579	25.10	23.93–26.28	540	21.79	20.49–23.09	1,119	23.52	22.66–24.38
P_{trend}[b]			0.01			6×10^{-5}			3×10^{-6}	
$P_{interaction}$ rs16969968 × sex[b]			0.51			0.99			0.86	

[a]Means were adjusted for age, study site, sex, and case–control status when appropriate in ever smokers only.
[b]CPD was log transformed in linear regression where SNP genotypes were coded as counts of minor allele (0/1/2) adjusting for age, study site, sex, and case–control status when appropriate. For the test of interaction, the interaction term of rs16969968 × sex was added to the initial model.

associated with CPD ($P = 1 \times 10^{-6}$), with rare homozygotes ever smoking carriers smoking 1.72 CPD more than common homozygotes. There was little evidence for a sex difference in the effect of the rs16969968 variant on CPD, with male and female smoking variant carriers smoking approximately the same amount more (male and female rare homozygotes smoked 1.79 and 1.29 CPD more than common homozygotes, respectively; $P_{het} = 0.86$; Table 2). Similar patterns were observed in cases and controls when analyzed separately ($P_{het} = 0.51$ and 0.99, respectively).

Discussion

This study has replicated our previous observation of a sex difference in the association between the 15q25 variant rs16969968 and UADT cancers. In a combined analysis, the association was highly significant in women ($P = 7 \times 10^{-6}$) but not men ($P = 0.35$) with strong evidence for heterogeneity ($P_{het} = 10^{-4}$) arguing against a chance finding. Under the hypothesis that the association between the rs16969968 variant and tobacco-related pathologies is mediated by this variant's effect on propensity to smoke, an association in UADT cancers, and particularly in laryngeal cancers, would be expected. However, the observation of a sex difference in the association with UADT cancers is intriguing for several reasons. Firstly, extrapolating from the observed effect of rs16969968 on CPD, only a small OR of approximately 1.02 for UADT cancers is expected in both men and women (Supplementary Method and Supplementary Table S2). This corresponds closely with observation of association between UADT cancers and rs16969968 in men but risk observed in women is much higher. Secondly, as reported here (Table 2) and elsewhere (4, 6), there is little evidence for a sex difference in the association between rs16969968 and CPD. This association could be potentially caused by a sex difference in the association between the 15q25 variant and smoking propensity not captured by the crude smoking measures available to this study. Nevertheless, if this association was caused by such a sex difference in propensity to smoke, one might expect the sex difference in this association to manifest more strongly in a cancer such as lung cancer, where the risks associated with tobacco consumption are more pronounced. However, to date, there is only inconsistent evidence for a sex difference in the association between this 15q25 variant and lung cancer (9–11). This seems to imply that rs16969968 has additional effects on UADT cancer susceptibility than just increasing propensity to smoke, as has been suggested for lung cancer (2, 9–11).

nAChRs are expressed throughout the UADT and have been shown to mediate pathobiological effects of tobacco and nicotine derivatives in the stratified epithelium lining the upper digestive tract (16–19). The rs16969968 SNP causes a change in amino acid 398 from asparagine (encoded by the *G* allele) to aspartic acid (encoded by *A* allele) in the second intracellular loop of the α5 subunit, and there is some evidence to suggest that this change alters nAChR function in response to nicotine agonist

in vitro (20). However, the functional consequences of this alteration in UADT carcinogenesis remain to be established.

In our study, the strongest association with 15q25 variant was observed among female laryngeal cancer. The male-to-female ratio in laryngeal cancer is 4.7:1 in America (21) and 11.3:1 in Europe (22), one of the highest among all cancer sites. It is worth noting that the difference in susceptibility to larynx cancer based on gender has remained unchanged through the years despite the increasing tobacco and alcohol consumption among women. The larynx is influenced by sexual hormones during the fetal development, as well as puberty and adulthood as it is subject to laryngeal epithelial layer modifications, cartilage metaplasia, and morphostructural changes (23, 24). These considerations, in association with the epidemiologic evidence, have led to the speculation that sex hormones might be involved in the carcinogenesis process (25). Our finding of sex-specific effect of 15q25 variant may add to the knowledge in understanding the underlying mechanism of sex difference in susceptibility to laryngeal cancer. Although speculative, there has been some data linking nAChR signaling to sex hormones. For example, some studies have shown that steroid hormones, including progesterone, are noncompetitive antagonists of nAChR (26, 27). In addition, a putative progesterone responsive element was found to be present in the promoter of α5 nAChR subunit, and progesterone has been shown to have an effect on α5 expression level both *in vitro* and *in vivo* (28). It is biologically plausible that the interplay between sex hormones and α5-containing nAChR may play a direct or indirect role in mediation of sex difference in susceptibility to laryngeal cancer. Nevertheless, such speculation needs to be further tested in in-depth molecular mechanistic studies in the future.

Several limitations are present in this pooled study. First, the observed sex-specific association could potentially be caused by a difference in variant frequency in controls between sexes (e.g., caused by, population stratification or a sex-specific ascertainment bias due to pathology type in hospital-based studies). However, there was little difference in the frequency of rs16969968 variant between male and female controls in any of the studies (Supplementary Table S3). Second, the information on human papillomavirus (HPV) infection, involved in the etiology of UADT cancers, particularly orophayrngeal cancers (29), was not available in our study. Interestingly, there was little evidence for an association between 15q25 variant and oropharyngeal cancer. Further studies including HPV infection status may help to clarify whether the effect of 15q25 variant are different in HPV-positive and HPV-negative oropharyngeal cancers.

In summary, this study has replicated the association between 15q25 variant rs16969968 and risk of UADT cancers in women, particularly prominent for laryngeal cancer. By contrast, there is little effect in men, implying a sex-specific effect. The biological basis for this association remains unclear and additional study appears warranted to further validate and explore these findings.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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