RESEARCH ARTICLE

Family History of Cancer and Head and Neck Cancer Risk in a Chinese Population

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Abstract

Background: The aim of this study was to investigate whether family history of cancer is associated with head and neck cancer risk in a Chinese population. Materials and Methods: This case-control study included 921 cases and 806 controls. Recruitment was from December 2010 to January 2015 in eight centers in East Asia. Controls were matched to cases with reference to sex, 5-year age group, ethnicity, and residence area at each of the centers. Results: We observed an increased risk of head and neck cancer due to first degree family history of head and neck cancer, but after adjustment for tobacco smoking, alcohol drinking and betel quid chewing the association was no longer apparent. The adjusted OR were 1.10 (95% CI=0.80-1.50) for family history of tobacco-related cancer and 0.96 (95%CI=0.75-1.24) for family history of any cancer with adjustment for tobacco, betel quid and alcohol habits. The ORs for having a first-degree relative with HNC were higher in all tobacco/alcohol subgroups. Conclusions: We did not observe a strong association between family history of head and neck cancer and head and neck cancer risk after taking into account lifestyle factors. Our study suggests that an increased risk due to family history of head and neck cancer may be due to shared risk factors. Further studies may be needed to assess the lifestyle factors of the relatives.

Keywords: Head and neck cancer - family history of cancer

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Introduction

In 2012, approximately 599,600 head and neck cancer (HNC) cases were diagnosed and 324,000 deaths due to head and neck cancer occurred (Ferlay et al., 2013). While alcohol drinking and tobacco smoking are the major risk factors for HNC, family history of cancer may also play an important role in the risk of HNC (Negri et al., 2009). The International Head and Neck Cancer Epidemiology (INHANCE) consortium reported that family history of HNC increased the risk of HNC by 1.68-fold (95% CI 1.23-2.29; 9,025 cases and 13,739 controls) with adjustment for multiple factors including tobacco and alcohol habits (Negri et al., 2009). Approximately, 5-10% HNC patients had family history of cancer according to this pooled data of studies, largely from Europe, the US and South America. Other studies using population-based genealogical resources in Utah, Iceland, and Sweden have also reported on an increased the risk of HNC due to family history of cancer (Li et al., 2003; Amundadottir et al., 2004; Teerlink et al., 2012). The limitation in these large-scale database studies is that there was no information on tobacco and alcohol thus it is difficult to assess whether the increased risk due to family history is because of shared

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genetics or shared lifestyle factors.

Previous case-control studies in China have investigated risk factors for HNC. A hospital based case-control study of 404 case-control pairs in Beijing included laryngeal cancer cases diagnosed between 1989-1990 and controls matched by age and gender (Zheng et al., 1990). A population-based case-control in Shanghai, China from 1988 to 1990, included 204 oral cancer cases and 414 controls (Zheng et al., 1992). They reported that of the oral squamous cell carcinoma cases, 34% were attributed to tobacco smoking and 24% were attributed to alcohol drinking. Family history of cancer was not investigated in these studies, to our knowledge. A more recent large case-control study of oral cancer reported that green tea consumption may be protective against oral cancer, particularly in men and in smokers (Fu et al., 2013). One study in the Liaoning province of China reported an OR of 2.0 (95%CI=1.3-3.2) for any family history of cancer among laryngeal cancer patients (288 cases and 298 controls) without adjustment and an OR of 2.3 (95%CI=1.2-4.5) for family history of malignancy after adjustment for various factors (Li et al., 2009).

The aim of our study is to investigate the association between family history of cancer and HNC risk in a Chinese population, with adjustments for shared lifestyle factors such as tobacco smoking and alcohol drinking.

Materials and Methods

This study in East Asia is a case-control study including eight centers (Beijing, Fujian, Henan, Jiangsu, Liaoning, Shanghai, Sichuan, and Taiwan). Between December 2010 to November 2013, 921 incident cases of HNC cases, including oral cavity, oropharynx hypopharynx larynx and 806 controls were recruited. The interview of both cases and controls were structured to obtain information on current and previous alcohol consumption, dietary habits, tobacco consumption and other lifestyle factors. Blood samples were collected from cases and controls whenever possible. Written consent for participation was obtained from all study participants. Ethical approval for human subject research was obtained at the University of Utah, Fujian, Henan, Shanghai, Sichuan, Taiwan, and Beijing.

The inclusion criteria for cases were 1) age 18-80 years, 2) incident cases of HNC (tumors were assigned to one of the five categories as follows: (1) oral cavity (includes lip, tongue, gum, floor of mouth, and hard palate): codes C00.3 to C00.9, C02.0 to C02.3, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C06.0 to C06.2, C06.8, and C06.9; (2) oropharynx (includes base of tongue, lingual tonsil, soft palate, uvula, tonsil, and oropharynx): codes C01.9, C02.4, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0 to C10.4, C10.8, and C10.9; (3) hypopharynx (includes pyriform sinus and hypopharynx):codes C12.9, C13.0 to C13.2, C13.8, and C13.9; (4) oral cavity, pharynx unspecified or overlapping: codes C02.8, C02.9, C05.8, C05.9, C14.0, C14.2, and C14.8; and (5) larynx (includes glottis, supraglottis, and subglottis): codes C32.0 to C32.3 and C32.8 to C32.9), 3) final diagnosis based on histological or cytological confirmation, and 4) interviews performed within six months of cancer diagnosis. Controls were frequency-matched by sex, 5-year age group, ethnicity, and residence area from hospitals at each of the centers. The proportion of hospital controls within a particular diagnostic group did not exceed 33%. Hospital controls were in the hospital for less than one month when recruited. In the final analysis dataset, there were 921 cases (424 oral cavity, 106 oropharynx, 81 hypopharynx, 85 larynx, and 225 unspecified or overlapping) and 806 controls.

The number of brothers and sisters, the number of first-degree relatives (parent, siblings, and children) with a history of cancer, the site of the cancer and the type of affected relative were included in information on family history. A subject with a family history for a given cancer was considered if at least one affected first-degree relative was reported by the subject.

Statistical Methods. The odds ratios (OR) and 95% confidence intervals (CI) were estimated using logistic regression. The adjustment variables included center, age (categories as shown in Table 1), sex, education (categories as shown in Table 1), cigarette smoking (categorical packyears, never smoker/1-19/20-39/≥40), alcohol drinking frequency (never, <2 drinks/day, ≥2 drinks/day), number of sisters, and number of brothers where appropriate. We assessed family history of HNC, tobacco-related cancers (lung, nasopharynx, nasal cavity, paranasal sinuses, esophagus, stomach, pancreas, liver, kidney, urinary bladder, uterine cervix, bone marrow (IARC, 2012), and any cancer. We additionally adjusted on years of betel quid use for the analysis of family history of head and neck cancer.

Results

The demographic characteristics of 921 cases and 806 controls in the case-control study are presented in Table I. Taiwan contributed a large number of cases (482 cases, 52.3%). There were more male cases (726 cases, 78.8%) compared to female cases, and more cases with oral cavity cancer compared to other cancer sites.

In the crude model, we observed a 3.45-fold increase in the risk of HNC due to family history of HNC (Table 2). The strong association was not observed after we adjusted for center, age, sex, tobacco smoking, alcohol drinking, betel quid chewing and number of brothers and sisters. None of the female controls had family history of HNC, thus we did not estimate odds ratios for this subgroup. When comparing cancer sites, the risk due to family history of HNC was strong for oral cavity, hypopharynx cancers as well as cancers in overlapped HNC sites in the crude analysis but not after adjustment for lifestyle factors.

Family history of tobacco-related cancers conferred an OR of 1.37 (95%CI=1.04-1.81) in the crude model, but when adjusted for tobacco smoking, alcohol drinking and other factors, the association was no longer statistically significant (Table 3).

Also, the OR was 1.70 (95% CI=1.00-2.89) for family history of tobacco-related cancer due to relative with the cancer diagnosis <50 years in the crude model, but

after adjustment for confounders, the association was not observed. There was an increased risk observed for siblings being the type of affected relative for family history of tobacco-related cancers even after adjustment for tobacco and alcohol (OR=1.65, 95%CI=1.02-2.68).

Family history of any cancer was not associated with HNC risk (Table 4) when taking into account tobacco smoking and alcohol drinking. The odds ratios for family

Table 1. Demographic Characteristics of Head and Neck Cancer Cases and Controls

	Cases n	(%)	Controls n	(%)	p-value
Total	921		806		
Center					<0.0001
Beijing	54	5.9	52	6.5	
Jiangsu	63	6.8	77	9.5	
Shanghai	55	6.0	56	6.9	
Henan	26	2.8	44	5.5	
Fujian	60	6.5	50	6.2	
Liaoning	57	6.2	75	9.3	
Sichuan	124	13.5	51	6.3	
Taiwan	482	52.3	401	49.8	
Age					<0.0001
<45 years old	146	15.9	257	31.9	
45-<55 years old	273	29.6	215	26.7	
55-<65 years old	297	32.2	222	27.5	
65+ years old	205	22.3	112	13.9	
Sex					<0.0001
Male	726	78.8	556	69.0	
Female	195	21.2	250	31.0	
Education					<0.0001
Illiterate	59	6.4	24	3.0	
Primary school	228	24.8	129	16.0	
Junior/middle school	261	28.3	150	18.6	
Senior/high school	244	26.5	170	21.1	
College/university and above	129	14.0	333	41.3	
Subsite					<0.0001
Oral cavity	424	46.0			
Oropharynx	106	11.5			
Hypopharynx	81	8.8			
Larynx	85	9.2			
Unspecified or overlapping	225	24.5			

Table 2. Family History of Head and Neck Cancer and the Risk of Head and Neck Cancer

	No Cases	Yes Controls	Cases	Controls	Crude OR	(95%CI)	Adjusted OR*	(95%CI)
Family history of HNC	894	799	27	7	3.45	(1.49-7.96)	1.47	(0.39-5.53)
Probands' sex								
Male	703	549	23	7	2.57	(1.09-6.02)	1.38	(0.34-5.59)
Female	191	250	4	0	-----	-----	-----	-----
Probands' age								
<50 years	252	385	7	5	1.99	(0.62-6.34)	0.22	(0.01-7.56)
≥50 years	642	441	20	2	6.87	(1.60-29.54)	2.67	(0.50-14.27)
Relative with the cancer								
< 50 years	894	799	11	2	4.91	(1.09-22.23)	1.40	(0.72-27.3)
≥50 years	894	799	16	5	2.86	(1.04-7.84)	1.47	(0.34-6.32)
Probands' cancer site								
Oral cavity	410	799	14	7	3.90	(1.56-9.73)	2.72	(0.59-12.48)
Oropharynx	103	799	3	7	3.33	(0.85-13.06)	4.73	(0.80-27.97)
Hypopharynx	78	799	3	7	4.39	(1.11-17.32)	0.36	(0.02-8.76)
Larynx	84	799	1	7	1.36	(0.17-11.18)	0.81	(0.01-22.3)
Overlapping	219	799	6	7	3.12	(1.04-9.39)	0.45	(0.03-6.32)
Type of affected relative								
Parents	894	799	13	5	2.32	(0.82-6.54)	1.27	(0.27-6.10)
Siblings	894	799	18	3	5.36	(1.57-18.26)	2.14	(0.17-27.7)
Sex of affected relative								
Male	894	799	22	6	3.28	(1.32-8.12)	1.30	(0.23-7.43)
Female	894	799	8	4	1.79	(0.54-5.96)	1.74	(0.24- 12.35)

*Adjusted for center, age, sex, tobacco smoking (packyear categories), alcohol drinking (frequency), betel quid chewing years, number of sisters, number of brothers

Table 3. Family History of Tobacco-Related Cancer and the Risk of Head and Neck Cancer

	No Cases	Yes Controls	Cases	Controls	Crude OR	(95%CI)	Adjusted OR*	(95%CI)
Family history of HNC	777	710	144	96	1.37	(1.04-1.81)	1.10	(0.80-1.50)
Probands' sex								
Male	609	478	117	78	1.18	(0.86-1.61)	1.03	(0.72-1.46)
Female	168	232	27	18	2.07	(1.11-3.88)	1.41	(0.72-2.78)
Probands' age								
<50 years	228	337	31	26	1.76	(1.02-3.05)	1.07	(0.55-2.06)
≥50 years	549	373	113	70	1.10	(0.79-1.52)	1.12	(0.78-1.60)
Relative with the cancer								
< 50 years	777	710	41	22	1.70	(1.00-2.89)	1.54	(0.87-2.72)
≥50 years	777	710	103	74	1.27	(0.93-1.74)	1.02	(0.72-1.45)
Probands' cancer site								
Oral cavity	355	710	69	96	1.44	(1.03-2.01)	1.15	(0.80-1.67)
Oropharynx	89	710	17	96	1.41	(0.81-2.48)	0.89	(0.47-1.70)
Hypopharynx	67	710	14	96	1.55	(0.84-2.86)	0.77	(0.32-1.87)
Larynx	75	710	10	96	0.99	(0.49-1.97)	1.27	(0.56-2.88)
Overlapping	191	710	34	96	1.32	(0.86-2.01)	1.15	(0.73-1.82)
Type of affected relative								
Parents	777	710	96	81	1.08	(0.79-1.48)	0.88	(0.62-1.25)
Siblings	777	710	69	29	2.17	(1.39-3.39)	1.65	(1.02-2.68)
Sex of affected relative								
Male	777	710	113	75	1.37	(1.01-1.88)	1.13	(0.80-1.59)
Female	777	710	55	33	1.52	(0.98-2.37)	1.18	(0.72-1.93)

*Adjusted for center, age, sex, tobacco smoking (packyear categories), alcohol drinking (frequency), number of sisters, number of brothers

history of HNC with tobacco and alcohol consumption are presented in Figure 1.

The OR, for having a first-degree relative with HNC was higher in tobacco/alcohol subgroups; increasing from 2.10 to 2.95 in users of tobacco only, and from 5.33 to 16.73 in alcohol and tobacco users. The p-value of interaction for family history of HNC with smoking and drinking habits was 0.5303. The corresponding p-values of interaction for tobacco, alcohol were 0.3309 with family history of tobacco related cancers and 0.9781 with family history of all cancers.

Discussion

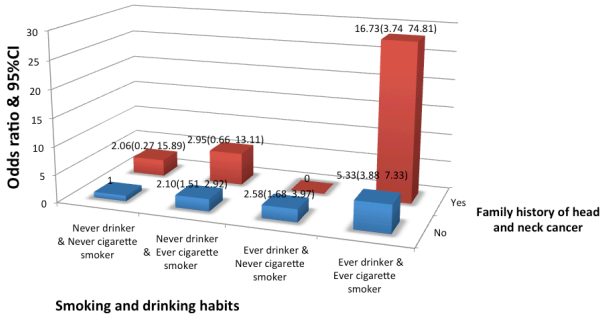

Figure 1. Odds Ratios for Family History of Head and Neck Cancers by Alcohol and Tobacco Consumption. Adjusted for center, age, sex, number of sisters and brothers

Table 4. Family History of Cancer and Risk of Head and Neck Cancer

	No Cases	Yes Controls	Cases	Controls	Crude OR	(95%CI)	Adjusted OR*	(95%CI)
Family history of cancer	590	567	254	197	1.24	(1.00-1.54)	0.96	(0.75-1.24)
Probands' sex								
Male	451	365	206	158	1.06	(0.82-1.35)	0.87	(0.65-1.17)
Female	139	202	48	39	1.79	(1.11-2.88)	1.31	(0.77-2.22)
Probands' age								
<50 years	181	286	58	68	1.35	(0.91-2.00)	1.00	(0.61-1.64)
≥50 years	409	281	196	129	1.04	(0.80-1.37)	0.98	(0.72-1.32)
Relative with the cancer								
<50 years	590	567	75	54	1.34	(0.92-1.93)	1.12	(0.74-1.70)
≥50 years	590	567	17	143	1.20	(0.93-1.53)	0.95	(0.71-1.26)
Probands' cancer site								
Oral cavity	286	567	125	197	1.26	(0.97-1.64)	0.94	(0.69-1.28)
Oropharynx	67	567	29	197	1.25	(0.78-1.98)	0.84	(0.48-1.46)
Hypopharynx	42	567	24	197	1.65	(0.97-2.79)	0.76	(0.33-1.72)
Larynx	49	567	14	197	0.82	(0.44-1.52)	0.89	(0.42-1.88)
Overlapping	146	567	62	197	1.22	(0.87-1.72)	1.06	(0.73-1.54)
Type of affected relative								
Parents	590	567	169	148	1.10	(0.86-1.41)	0.90	(0.67-1.20)
siblings	590	567	11	66	1.62	(1.17-2.24)	1.12	(0.78-1.63)
Sex of affected relative								
Male	590	567	169	129	1.26	(0.97 1.63)	1.02	(0.76-1.37)
Female	590	567	115	87	1.27	(0.94 1.72)	0.96	(0.67-1.36)

*Adjusted for center, age, sex, tobacco smoking (packyear categories), alcohol drinking (frequency), number of sisters, number of brothers

Previous studies have reported that family history of HNC in first-degree relatives increased the risk of HNC. Our results support the association between family history of HNC in first-degree relatives and the risk of HNC, but with adjustment for tobacco, betel quid and alcohol habits the association was not persistent.

While the INHANCE consortium results showed that the HNC risk was higher for more distal sites (hypopharynx OR=2.28, 95%CI=1.4-3.54 and larynx OR=2.07, 95%CI=1.57-2.73), the crude estimates in our study suggest that the HNC risk was higher in the hypopharynx and oropharynx. However, our study sample size is smaller and thus the confidence intervals were fairly wide, making these comparisons difficult. In the Utah population, for first-degree relatives of a cancer patient, the RRs for cancer of the same site were 6.0 (95% CI 2.37-12.65) for tongue cancer, 7.9 (95% CI 3.46-15.67) for pharyngeal cancer, and 5.0 (95% CI 2.59-8.65) for laryngeal cancer (Teerlink et al., 2012). In the Swedish Family Cancer database, the standardized incidence ratios (SIRs) for upper aerodigestive tract cancer in offspring by parental cancer was 1.40 (95%CI=0.98-1.95) for head and neck cancers (Li et al., 2003). In the Icelandic population, for first-degree relatives of a cancer patient, the RRs for cancers of the same site were 5.04 (95% CI 2.75-9.52) for lip cancer, 3.02 (95% CI 1.06-6.65) for larynx cancer (Amundadottir et al., 2004). Differences in risk due to the head and neck cancer subsite may be difficult to discriminate, even in large-scale studies.

Although family history of tobacco-smoking-related cancer was associated with a modest increase in risk (OR= 1.11, 95% CI 1.01-1.23) in the INHANCE analysis, we did not observe a clear association with family history of tobacco-related cancers or with family history of cancer in general. In the Utah population, first degree relatives of had increased risks of laryngeal cancer (Negri et al., 2009). In the Icelandic population, first degree relatives of esophageal, lip, lung and pharyngeal cancer had an increased risk of laryngeal cancer; first degree relatives of breast, cervical, and lung cancers had a increased risk of pharyngeal cancer; and first degree relatives of anal, esophageal, lip and lung cancer had an increased risk of tongue cancer. Although family history of tobacco-related cancers may increase the risk of head and neck cancers, the relative risks are generally lower than those for family history of head and neck cancer. Our study may not have had an enough statistical power to detect an association.

In our study, the interaction analysis was suggestive of a higher risk of HNC due to family history of head and neck cancer among tobacco and alcohol users, although the p-value for interaction was not significant. In the INHANCE analysis, the odds ratio increased from 3.34 (95% CI 2.90-3.86) to 7.21 (95% CI 5.46-9.54) for both tobacco and alcohol users. In our study, the odds ratio increased from 5.33(95%CI=3.88-7.33) to 16.73 (95%CI=3.74-74.81). Similar to the INHANCE analysis, we did not observe a statistically significant association between family history of HNC and HNC risk among never drinkers and never cigarette smokers.

There are several possible limitations in this study. Recall bias is a potential limitation since patients had already been diagnosed with cancer and may have recalled family history more carefully. It seems unlikely that cases or controls would forget to report on any incident cases of family history of cancer in their first degree relatives. Although we had information about first-degree relatives, we did not have information on cancer among second- or third-degree relatives. Due to the small number of subjects with family history of cancer, we had lower statistical power to detect moderate risks and we were unable to estimate some odds ratios in a stratified analysis. Having information on whether the relatives smoked tobacco or drank alcohol would have been of interest to further clarify whether associations with family history of cancer were due to shared lifestyle habits.

The key strengths of the study include the fairly large sample size of 921 cases and 806 controls in our case-control study. Another strength of our study is the detailed tobacco, betel quid and alcohol information, which allowed us to adjust on lifestyle factors that may contribute to the association between family history of cancer and cancer risk. We were also able to explore potential effect modification, i.e., the impact of family history of HNC stratified by tobacco and alcohol. Also, in this case-control study, we adjusted for the number of brothers and sisters in the assessment of the associations. Finally, to our knowledge, this is the first investigation of family history of HNC in an East Asian population.

In conclusion, we observed a four-fold increase in the risk of head and neck cancer due to family history of head and neck cancer but after adjustment for lifestyle factors the association was no longer observed. Family history of tobacco-related cancers and cancer in general were also not associated with an increased risk of head and neck cancer after adjustment for tobacco and alcohol habits. Our results support that shared lifestyle factors in a family are likely to play an important role for head and neck cancer risk due to family history of cancer. Further large scale studies in this population may be needed to further discern risk differences due to family history of head and neck cancer, for the head and neck cancer subsites and to assess effect modification due to tobacco and alcohol habits.

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