Cancer Epidemiology 60 (2019) 208–215

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Body mass index and the risk of head and neck cancer in the Chinese population

Yuji Chen[a], Yuan-Chin Amy Lee[a], Shuang Li[a], Qian Li[b], Chien-Jen Chen[c,d], Wan-Lun Hsu[c], Pen-Jen Lou[e], Cairong Zhu[f], Jian Pan[g], Hongbing Shen[h], Hongxia Ma[h], Lin Cai[i], Baochang He[i], Yu Wang[j,k], Xiaoyan Zhou[k,l], Qinghai Ji[j,k], Baosen Zhou[m], Wei Wu[m], Jie Ma[n], Daisuke Kawakita[a,o], Paolo Boffetta[p], Zuo-Feng Zhang[q], Min Dai[r], Mia Hashibe[a,*]

[a] Division of Public Health, Department of Family and Preventive Medicine, University of Utah School of Medicine and Huntsman Cancer Institute, Salt Lake City, UT, USA
[b] Department of Preventive Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[c] Genomics Research Center, Academia Sinica, Taipei, Taiwan
[d] Graduate Institute of Epidemiology and Preventive Medicine, National Taiwan University, Taipei, Taiwan
[e] Department of Otolaryngology, National Taiwan University Hospital, Taipei, Taiwan
[f] Department of Epidemiology and Biostatistics, West China School of Public Health, Sichuan University, Sichuan, China
[g] Department of Oral Surgery, West China Hospital of Stomatology, Sichuan University, Sichuan, China
[h] Department of Epidemiology and Biostatistics, Jiangsu key lab of Cancer Biomarkers, Prevention and Treatment, Collaborative Innovation Center for Cancer Personalized Medicine, School of Public Health, Nanjing Medical University, China
[i] Department of Epidemiology and Biostatistics, School of Public Health, Fujian Medical University, Fujian, China
[j] Department of Head and Neck Surgery, Fudan University Shanghai Cancer Center, Shanghai, China
[k] Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China
[l] Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai, China
[m] Department of Epidemiology, School of Public Health, China Medical University, Liaoning, China
[n] Department of Head & Neck Oncology, Henan Cancer Hospital, Henan, China
[o] Department of Otorhinolaryngology, Head and Neck Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan
[p] Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York City, NY, USA
[q] Department of Epidemiology and Center for Environmental Genomics, UCLA Fielding School of Public Health, Los Angeles, CA, USA
[r] National Office of Cancer Prevention & Control Cancer Institute & Hospital, and Chinese Academy of Medical Sciences, Beijing, China

ARTICLE INFO

Keywords:
BMI
Head and neck cancer risk
East Asia

ABSTRACT

Objective: To investigate potential associations between body mass index (BMI) and head and neck cancer (HNC) risk in an East Asian population.

Methods: We conducted a hospital-based multicenter case-control study in East Asia including 921 cases and 806 controls. We estimated the odds ratios (ORs) and 95% confidence intervals (95% CI) for HNC risks by using logistic regression, adjusting on potential confounders.

Results: Compared to normal BMI at interview (18.5– < 25 kg/m^2), being underweight (BMI < 18.5 kg/m^2) was associated with a higher HNC risk (OR = 2.71, 95% CI 1.40–5.26). Additionally, obesity (BMI > 30 kg/m^2) was associated with a lower HNC risk (OR = 0.30, 95% CI 0.16–0.57). Being underweight at age 20 was also associated with an increased risk of HNC. However, being underweight at 5 years or 2 years before interview was not associated with a higher risk of HNC.

Conclusion: We observed an inverse association between BMI and HNC risk, which is consistent with previous studies in other geographic regions. Being underweight at age 20 was also associated with a higher risk of HNC, suggesting that reverse causality was not the main source of the association.

* Corresponding author at: Division of Public Health, Department of Family & Preventive Medicine, Huntsman Cancer Institute, University of Utah School of Medicine, 2000 Circle of Hope, Salt Lake City, UT, 84112, USA.
E-mail address: mia.hashibe@utah.edu (M. Hashibe).

https://doi.org/10.1016/j.canep.2019.04.008
Received 4 December 2018; Received in revised form 10 April 2019; Accepted 25 April 2019
Available online 07 May 2019

1. Introduction

According to GLOBOCAN, about 706,000 cases of head and neck cancer (HNC, comprised of cancers of the oral cavity, oropharynx, hypopharynx and larynx) and 358,000 deaths occurred due to HNC in the world in 2018 [1,2]. In China, approximately 68,000 cases of HNC were diagnosed, and 36,000 deaths occurred due to HNC each year [1,2]. The estimated HNC age-standardized rate (ASR) in China was 3.1/100,000, which is lower than the ASR of 9.6/100,000 in regions with very high human development index [1,2]. However, few studies of HNC have been conducted in China.

Tobacco smoking and alcohol consumption are major risk factors for HNC, and human papilloma virus plays a major role in oropharyngeal cancer risk [3–5]. More than half (52.9%) of men smoke cigarettes in China according to the Global Adult Tobacco Survey (GATS) in China in 2010 [6], but the incidence of HNC among men in China is 4.9/100,000, which is relatively low compared to the incidence of HNC (12.8/100,000) among men in the world [1,2]. Meanwhile, other factors associated with HNC risk are of concern since some patients are non-smokers and non-drinkers [3–5].

Most studies in Europe and North America reported that lower Body mass index (BMI) was associated with a higher risk of HNC, compared to normal BMI [3,7–14]. Additionally being overweight and obese was associated with a decreased risk of HNC compared to normal weight [9]. In a pooled analysis of 17 studies from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium including 12,716 cases and 17,438 controls, compared to normal BMI, having a low BMI was associated with a higher risk of HNC (OR = 2.13, 95%CI 1.75–2.58), and being overweight or obese was associated with a lower risk [3]. For individuals who were ever smokers and drinkers, the same inverse association was observed (OR = 2.01, 95%CI 1.60–2.52 for underweight; OR = 0.38, 95%CI 0.30 − 0.49 for overweight) [3]. However, such an association with BMI was not detected in never smokers and never drinkers (OR = 3.13, 95%CI 0.73–13.40 for underweight at interview; OR = 0.93, 95%CI 0.49–1.80 for overweight at interview; OR = 0.95, 95%CI 0.47–1.91 for obesity at interview) in this INHANCE pooled analysis [3]. The only study on BMI and HNC risk in China reported a hazard ratio of 0.84 (95%CI 0.49–1.41) for the risk of HNC with every 5 kg/m^2 increase in BMI among female never smokers and a hazard ratio of 2.33 (95%CI 0.64–8.45) among male never smokers [7].

Most of the previous large-scale studies investigating BMI and HNC risk focused on European-origin populations. The aim of this study was to investigate the role of BMI on HNC risk in an East Asian population, adjusting for potential confounders, including cigarettes smoking, alcohol drinking, and education. In addition, we aimed to explore the role of BMI at a young age and of BMI change throughout lifetime.

2. Materials and methods

2.1. Study design and population

We conducted a multicenter case-control study in East Asia. Between December 2010 and February 2015, 921 incident HNC cases, including oral cavity, oropharynx, hypopharynx and larynx, and 806 controls were recruited in eight centers (Beijing, Fujian, Henan, Jiangsu, Liaoning, Shanghai, Sichuan, and Taiwan). The participation rates were 85% for cases and 97% for controls. Face-to-face interviews of both cases and controls were structured to obtain information on current and previous alcohol consumption, dietary habits, tobacco consumption including cigarette, pipe, betel quid and tobacco and other lifestyle factors. Written consents for participation were obtained from all study participants. Ethical approval for human subject research was obtained at the University of Utah (University of Utah IRB no. 00041033 11/10/2010), Fujian (Fujian IRB 3/10/2011), Henan (Henan Cancer Hospital 2011), Shanghai (Fudan University IRB no. 101293-15 12/27/2010), Sichuan (Sichuan University IRB 9/29/2010), Taiwan (National Taiwan University Hospital no. 201006077R 8/10/2010), and Beijing (Chinese Academy of Medical Sciences 2012).

The inclusion criteria for cases were 1) age 18–85 years, 2) incident case of HNC, including the following categories (ICD-0-2): (i) oral cavity (including 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; (ii) oropharynx (including 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, C10.2 to C10.4, C10.8, and C10.9; (iii) hypopharynx (including pyriform sinus and hypopharynx):codes C12.9, C13.0 to C13.2, C13.8, and C13.9; (iv) oral cavity, pharynx unspecified or overlapping sites: codes C02.8, C02.9, C05.8, C05.9, C14.0, C14.2, and C14.8; and (v) larynx (including 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. Hospital controls were randomly chosen from subjects admitted as in-patients or out-patients in the same hospital as the cases, and they were in the hospital for less than one month when recruited. Controls were frequency-matched by sex, 5-year age group, ethnicity, and residence area from hospitals at each of the centers; they were selected among patients with a defined list of non-chronic diseases unrelated to alcohol, tobacco, or dietary practices. The proportion of controls within a particular diagnostic group did not exceed 33%; These groups were 1) benign tumor disorders [D10-D36] (27.3%), 2) endocrine and metabolic disorders [E00-E07, E24-E27] (4.6%), 3) skin, subcutaneous tissue, and musculoskeletal disorders [M05-M06, M15-M19, M50, M51, M53, M54, N60, L04.0, L05, L21, L60.0, L72.0, R22] (0.2%), 4) trauma [S00-T98] (1.1%), 5) circulatory disorders [I83] (0.2%), 6) ear, eye and mastoid disorders [H00-H24, H27, H29-H95, except H36.0] (0.1%), 7) diseases of upper-respiratory tract [J30-J39] (1.5%), 8) diseases of the oral cavity, salivary gland and jaws [K01-K02] (10.9%), 9) gastro-intestinal disorders [K35-K38, K40-K46, K50-K52, K55-K63, K80, K81, K83.0] (5.0%), 10) disorders of the nervous system [G00-G19, G23-G99] (0.1%), 11) other diseases [A49.9, I10, J00, J02.9, Q87.0, Q89.2] (26.7%), and 12) no diagnosis (healthy population) (22.2%).

2.2. Statistical analyses

In this analysis, 921 cases (424 oral cavity, 106 oropharynx, 81 hypopharynx, 85 larynx, and 225 unspecified or overlapping) and 806 controls were included. We estimated the adjusted odd ratios (ORs) and 95% confidence intervals (95% CI) by using unconditional logistic regression with covariate adjustment and using SAS software 9.4 :ethnicity, age (categorical as shown in Table 1), sex, education (categorical as shown in Table 1), center, duration of cigarette smoking (0, 1–19, 20–39 or ≥ 40 years), average amount of smoking (0, 1–19, or ≥ 20 cigarette per day), duration of alcohol drinking (0, 1–19, 20–39 or ≥ 40 years), and amount of alcohol drinking (0, < 2, or ≥ 2 drinks per day). We also adjusted for betel quid chewing frequency (0, 1–9, 10–19 or ≥ 20 pieces per day) and duration of use (0, 1–19, 20–39 or ≥ 40 years).

Height and weight variables were self-reported and collected in questionnaire-based interviews. There were only three individuals with height missing and three individuals with weight missing. We calculated BMI as weight (kg) divided by height squared (m^2). In addition to weight at the time individuals were interviewed, we also collected information on weight 2 years and 5 years before interview and at age 20. BMI change was calculated as the difference between BMIs from two different periods divided by the BMI at the earlier period. Height was categorized into quartiles of the distribution of the study population (160 cm, > 160-167 cm, > 167-172 cm and > 172 cm). Height was also modeled as continuous variables. Trend tests were conducted with height and weight as both categorical variables and continues variables.

Table 1
Characteristics of cases and controls.

	Cases (n = 921)		Controls (n = 806)		Chi-square p-value
	n	%	n	%	
Age (years)					< .0001
18-44	146	15.9	257	31.9	
45-54	273	29.6	215	26.7	
55-64	297	32.2	222	27.5	
65-85	205	22.3	112	13.9	
Education					< .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	
Sex					< .0001
Male	726	78.8	556	69.0	
Female	195	21.2	250	31.0	
Center					< .0001
Beijing	54	5.9	52	6.5	
Jiangsu	63	6.8	77	9.6	
Shanghai	55	6.0	56	7.0	
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	
Ethnicity					< .0001
Han	556	60.4	407	50.5	
Other	365	39.6	399	49.5	
Ever smoke					< .0001
Never	319	34.6	462	57.3	
Ever	600	65.1	343	42.6	
Missing	2	0.2	1	0.1	
Ever drink					< .0001
Never	433	47.0	582	72.2	
Ever	486	52.8	224	27.8	
Missing	2	0.2	0	0	
Ever betel					< .0001
Never	624	67.8	761	94.4	
Ever	293	31.8	42	5.2	
Missing	4	0.4	3	0.4	
Subsite					< .0001
Oral cavity	424	46.0			
Oropharynx	106	11.5			
Hypopharynx	81	8.8			
Larynx	85	9.2			
Unspecified or overlapping	225	24.4			

Trend tests for ordered variables were performed by assigning the score j to the j-th exposure level of a categorical variable (where j_1, 2…) and treating it as a continuous predictor in unconditional logistic regression. Trend tests for continuous variables were conducted by treating the variable as a continuous predictor in unconditional logistic regression.

We conducted stratified analysis by cigarette smoking status, alcohol drinking status, betel chewing status, age (18–54, or 55–85), sex and cancer subsites to explore possible differences in association between subgroups. We also ran chi-square tests on fruit and vegetable intake and BMI at age 20 in order to investigate the BMI association with diet related intake and assess whether diet contributed to associations observed for BMI and HNC risk. The fruit/vegetable intake was categorized in to three groups (1–3 times per day, 3–6 times every week, and < 3 times every week or not at all).

Table 2
BMI, height, BMI change and the risk of head and neck cancer.

			Fully adjusted	
	Case	Control	OR[a]	95%CI
BMI at interview (kg/m^2)				
0 < BMI < 18.5 (underweight)	52	16	2.71	(1.40, 5.26)
18.5 ≤ BMI < 25 (normal weight)	522	511	1.00	
25 ≤ BMI < 30 (overweight)	222	204	0.87	(0.66, 1.15)
BMI ≥ 30 (obese)	38	41	0.30	(0.16, 0.57)
Missing	2	2		
p for trend				< .0001
BMI 2 years before interview (kg/m^2)				
0 < BMI < 18.5 (underweight)	27	24	1.12	(0.58, 2.17)
18.5 ≤ BMI < 25 (normal weight)	491	458	1.00	
25 ≤ BMI < 30 (overweight)	246	198	0.96	(0.72, 1.27)
BMI ≥ 30 (obese)	56	41	0.51	(0.28, 0.91)
Missing	16	53		
p for trend				0.0910
BMI 5 years before interview (kg/m^2)				
0 < BMI < 18.5 (underweight)	24	29	0.92	(0.48, 1.75)
18.5 ≤ BMI < 25 (normal weight)	492	457	1.00	
25 ≤ BMI < 30 (overweight)	239	194	0.97	(0.73, 1.29)
BMI ≥ 30 (obese)	54	35	0.52	(0.29, 0.95)
Missing	27	59		
p for trend				0.2060
BMI at age 20 (kg/m^2)				
0 < BMI < 18.5 (underweight)	85	72	1.51	(1.01, 2.24)
18.5 ≤ BMI < 25 (normal weight)	613	605	1.00	
25 ≤ BMI < 30 (overweight)	73	40	1.32	(0.81, 2.16)
BMI ≥ 30 (obese)	12	4	1.58	(0.43, 5.87)
Missing	53	53		
p for trend				0.5989
Height quantile				
Q1: height ≤ 160 cm	234	194	1.00	
Q2: 160 < height ≤ 167 cm	240	185	0.94	(0.66, 1.33)
Q3: 167 < height ≤ 172 cm	206	208	0.74	(0.50, 1.11)
Q4: height > 172 cm	154	186	0.74	(0.48, 1.14)
Missing	2	1		
p for trend				0.1194
BMI change from age 20 to 5 years before interview				
< −10% (BMI loss)	39	10	2.43	(1.07, 5.52)
−10%– < 10% (stable)	373	358	1.00	
≥ 10% (BMI gain)	355	305	1.07	(0.81, 1.41)
Missing	69	101		
p for trend				0.4982

[a] Adjusted for age, sex, ethnicity, education, center, daily cigarettes per day, cigarette years, alcohol drinks per week, alcohol years, betel quid chewed per day and betel years.

3. Results

Table 1 shows that most participants were between 45 and 64 years old and recruited from Taiwan and Sichuan. Cases were more likely to be male, to have smoked cigarettes and to drink alcohol, compared to controls.

Leanness (BMI < 18.5 kg/m^2) at the time of interview was associated with a higher risk of HNC (OR = 2.71, 95% CI 1.40–5.26; Table 2) compared to subjects with a normal BMI (18.5– < 25 kg/m^2). On the other hand, being obese (≥ 30 kg/m^2) was associated with a lower HNC risk (OR = 0.30, 95% CI 0.16 − 0.57). Being underweight at age 20 was also associated with a higher risk of HNC (OR = 1.51, 95% CI 1.01–2.24). No association was observed between leanness (BMI < 18.5 kg/m^2) at 2 years or 5 years before interview and the risk of HNC. However, obesity was consistently associated with a lower HNC risk. Height was not associated with head and neck cancer risk. Table 2 shows that BMI decreasing from age 20 to 5 years before interview (BMI decrease of < 10%) was associated with a higher HNC risk. However, BMI gain showed no association with HNC.

When stratified by cancer subsites, obesity was associated with

Table 3
BMI, height, BMI change and the risk of HNC by subsite.

	Oral cavity				Oropharynx				Hypopharynx				Larynx				Unspecified or overlapping			
	Ca	Co	OR[a]	95%CI	Ca	Co	OR[a]	95%CI	Ca	Co	OR[a]	95%CI	Ca	Co	OR[a]	95%CI	Ca	Co	OR[a]	95%CI
BMI at interview (kg/m^2)																				
0 < BMI < 18.5 (underweight)	19	16	1.96	(0.83,4.66)	7	16	3.38	(0.76,15.05)	7	16	13.50	(0.50,365.62)	4	16	19.58	(1.40,274.07)	15	16	2.97	(1.32,6.68)
18.5 ≤ BMI < 25 (normal weight)	232	511	1.00		61	511	1.00		47	511	1.00		54	511	1.00		128	511	1.00	
25 ≤ BMI < 30 (overweight)	115	204	1.11	(0.76,1.63)	26	204	0.78	(0.43, 1.42)	13	204	0.28	(0.11, 0.70)	15	204	0.55	(0.26, 1.15)	53	204	0.79	(0.52,1.21)
BMI ≥ 30 (obese)	23	41	0.33	(0.14,0.76)	2	41	0.05	(0.01, 0.33)	3	41	0.03	(0.01, 0.19)	0	41	–	–	10	41	0.27	(0.11,0.67)
p for trend				0.0664				0.0012				< .0001				0.0002				0.0004
BMI 5 years before interview (kg/m^2)																				
0 < BMI < 18.5 (underweight)	11	29	0.77	(0.32,1.85)	2	29	0.79	(0.12, 5.31)	2	29	4.39	(0.41, 46.64)	2	29	2.15	(0.30, 15.40)	7	29	1.15	(0.46,2.87)
18.5 ≤ BMI < 25 (normal weight)	220	457	1.00		63	457	1.00		43	457	1.00		51	457	1.00		115	457	1.00	
25 ≤ BMI < 30 (overweight)	124	194	1.10	(0.73,1.64)	21	194	0.68	(0.36, 1.31)	18	194	0.75	(0.32, 1.75)	16	194	0.70	(0.33, 1.49)	60	194	1.12	(0.74,1.70)
BMI ≥ 30 (obese)	26	35	0.43	(0.18,1.01)	5	35	0.25	(0.07, 0.92)	4	35	0.04	(0.01, 0.22)	2	35	0.16	(0.03, 0.91)	17	35	0.52	(0.23,1.17)
p for trend				0.5598				0.0415				0.0005				0.0257				0.4040
BMI at age 20 (kg/m^2)																				
0 < BMI < 18.5 (underweight)	37	72	1.23	(0.71,2.13)	4	72	0.60	(0.19, 1.89)	8	72	1.20	(0.39, 3.70)	5	72	1.67	(0.48, 5.81)	31	72	2.13	(1.29,3.52)
18.5 ≤ BMI < 25 (normal weight)	294	605	1.00		75	605	1.00		51	605	1.00		53	605	1.00		140	605	1.00	
25 ≤ BMI < 30 (overweight)	29	40	0.95	(0.46,1.99)	14	40	2.00	(0.89, 4.48)	6	40	0.98	(0.29, 3.37)	8	40	1.43	(0.51, 3.97)	16	40	1.12	(0.53,2.37)
BMI ≥ 30 (obese)	7	4	1.42	(0.28,7.21)	1	4	1.82	(0.16,21.31)	1	4	1.19	(0.06, 24.59)	2	4	19.20	(1.27,289.69)	1	4	0.68	(0.06,7.63)
p for trend				0.6808				0.0552				0.8512				0.3201				0.0262
Height quantile																				
Q1: height ≤ 160 cm	129	194	1.00		19	194	1.00		11	194	1.00		11	194	1.00		64	194	1.00	
Q2: 160 < height ≤ 167 cm	117	185	0.90	(0.57,1.41)	31	185	1.50	(0.69, 3.25)	19	185	1.01	(0.31, 3.33)	13	185	1.41	(0.45, 4.42)	60	185	0.94	(0.58,1.54)
Q3: 167 < height ≤ 172 cm	88	208	0.71	(0.41,1.22)	28	208	0.87	(0.36, 2.11)	19	208	0.71	(0.22, 2.32)	23	208	1.33	(0.41, 4.31)	48	208	0.66	(0.37,1.19)
Q4: height > 172 cm	55	186	0.51	(0.28,0.93)	18	186	0.78	(0.30, 2.05)	21	186	0.98	(0.29, 3.33)	26	186	1.70	(0.49, 5.91)	34	186	0.73	(0.38,1.39)
p for trend				0.0263				0.3236				0.8827				0.4376				0.2236
BMI change from age 20 to 5 years before interview																				
< −10% (BMI loss)	17	10	2.45	(0.84,7.18)	6	10	2.96	(0.73,11.98)	5	10	9.74	(1.12, 84.43)	5	10	10.81	(1.56, 75.01)	6	10	1.41	(0.40,5.02)
−10%− < 10% (stable)	169	358	1.00		60	358	1.00		33	358	1.00		39	358	1.00		72	358	1.00	
≥ 10% (BMI gain)	177	305	1.13	(0.78,1.64)	25	305	0.39	(0.21,0.74)	27	305	0.49	(0.21, 1.18)	23	305	1.10	(0.47, 2.57)	103	305	1.33	(0.88,2.00)
p for trend				0.8773				0.0005				0.0060				0.1985				0.2800

[a] Adjusted for age, sex, ethnicity, education, center, daily cigarettes per day, cigarette years, alcohol drinks per week, alcohol years, betel quid chewed per day and betel years.

Table 4
BMI, height, BMI change and the risk of HNC by cigarette smoking and drinking status.

	Never smoker				Ever smoker				Never drinker				Ever drinker			
	Ca	Co	OR[a]	95%CI	Ca	Co	OR[b]	95%CI	Ca	Co	OR[c]	95%CI	Ca	Co	OR[b]	95%CI
BMI at interview (kg/m^2)																
0 < BMI < 18.5 (underweight)	20	14	2.18	(0.97,4.87)	32	2	**6.41**	**(1.36,30.12)**	24	14	**2.25**	**(1.05,4.80)**	28	2	**5.68**	**(1.06,30.44)**
18.5 ≤ BMI < 25 (normal weight)	200	325	1.00		322	186	1.00		283	385	1.00		239	126	1.00	
25 ≤ BMI < 30 (overweight)	71	94	1.00	(0.66,1.53)	151	110	0.73	(0.5, 1.08)	103	147	0.89	(0.62, 1.27)	119	57	0.86	(0.54, 1.37)
BMI ≥ 30 (obese)	14	15	1.37	(0.55,3.42)	24	26	**0.10**	**(0.04,0.24)**	15	27	**0.42**	**(0.19,0.98)**	23	14	**0.17**	**(0.06,0.45)**
p for trend				0.6029				< .0001				0.0130				0.0009
BMI 2 years before interview (kg/m^2)																
0 < BMI < 18.5 (underweight)	10	17	1.01	(0.41,2.52)	17	7	1.34	(0.48, 3.72)	12	17	1.06	(0.45, 2.51)	15	7	1.26	(0.43, 3.71)
18.5 ≤ BMI < 25 (normal weight)	197	287	1.00		294	171	1.00		271	342	1.00		220	116	1.00	
25 ≤ BMI < 30 (overweight)	74	92	1.04	(0.68,1.62)	172	106	0.89	(0.60, 1.31)	115	145	0.96	(0.67, 1.36)	131	53	0.96	(0.59, 1.58)
BMI ≥ 30 (obese)	20	15	1.50	(0.61,3.69)	36	26	**0.21**	**(0.10,0.46)**	21	26	0.61	(0.28, 1.35)	35	15	**0.39**	**(0.16,0.92)**
p for trend				0.5257				0.0026				0.3545				0.1027
BMI 5 years before interview (kg/m^2)																
0 < BMI < 18.5 (underweight)	11	24	0.76	(0.33,1.76)	13	5	1.45	(0.46, 4.60)	12	24	0.72	(0.32, 1.62)	12	5	1.60	(0.47, 5.43)
18.5 ≤ BMI < 25 (normal weight)	189	277	1.00		303	180	1.00		263	335	1.00		229	122	1.00	
25 ≤ BMI < 30 (overweight)	80	95	1.06	(0.69,1.64)	159	99	0.87	(0.59, 1.30)	117	147	0.98	(0.69, 1.41)	122	47	0.96	(0.58, 1.60)
BMI ≥ 30 (obese)	20	10	1.93	(0.72,5.12)	34	25	**0.20**	**(0.09,0.43)**	22	19	0.72	(0.31, 1.68)	32	16	0.37	(0.15, 0.87)
p for trend				0.2294				0.0017				0.8984				0.0615
BMI at age 20 (kg/m^2)																
0 < BMI < 18.5 (underweight)	44	42	**2.69**	**(1.57,4.63)**	41	30	0.80	(0.44, 1.44)	53	54	**2.01**	**(1.25,3.22)**	32	18	0.73	(0.35, 1.52)
18.5 ≤ BMI < 25 (normal weight)	219	345	1.00		394	260	1.00		312	445	1.00		301	160	1.00	
25 ≤ BMI < 30 (overweight)	22	20	1.34	(0.58, 3.06)	51	20	1.21	(0.65, 2.28)	26	28	1.11	(0.56, 2.19)	47	12	1.74	(0.81, 3.77)
BMI ≥ 30 (obese)	4	2	1.23	(0.18, 8.37)	8	2	1.65	(0.25,11.06)	5	2	1.35	(0.21, 8.89)	7	2	1.58	(0.22,11.57)
p for trend				0.0192				0.2616				0.0496				0.0924
Height quantile																
Q1: height ≤ 160 cm	151	164	1.00		83	30	1.00		175	174	1.00		59	20	1.00	
Q2: 160 < height ≤ 167 cm	85	115	1.08	(0.70, 1.67)	155	70	0.82	(0.44, 1.53)	115	151	0.86	(0.58, 1.28)	125	34	1.19	(0.56,2.55)
Q3: 167 < height ≤ 172 cm	39	92	0.89	(0.49, 1.63)	167	116	0.64	(0.35, 1.17)	78	138	0.76	(0.46, 1.24)	128	70	0.82	(0.39,1.71)
Q4: height > 172 cm	30	78	0.94	(0.47, 1.88)	124	108	0.57	(0.30, 1.07)	57	111	0.77	(0.44, 1.36)	97	75	0.76	(0.35,1.65)
p for trend				0.8123				0.0477				0.3122				0.2514
BMI change from age 20 to 5 years before interview																
< −10% (BMI loss)	14	7	1.52	(0.51, 4.53)	25	3	4.06	(1.04,15.83)	18	10	1.74	(0.69, 4.44)	21	0	–	–
−10%− < 10% (stable)	125	214	1.00		248	144	1.00		176	255	1.00		197	103	1.00	
≥ 10% (BMI gain)	145	151	1.64	(1.10, 2.43)	210	154	0.68	(0.46,1.02)	192	224	1.45	(1.03, 2.04)	163	81	0.57	(0.35,0.96)
p for trend				0.0470				0.0035				0.1399				0.0019

[a] Adjusted for age, sex, ethnicity, education, center, alcohol drinks per week, alcohol years, betel quid chewed per day and betel years.
[b] Adjusted for age, sex, ethnicity, education, center, daily cigarettes per day, cigarette years, alcohol drinks per week, alcohol years, betel quid chewed per day and betel years.
[c] Adjusted for age, sex, ethnicity, education, center, daily cigarettes per day, cigarette years, betel quid chewed per day and betel years.

lower risk of oral cavity, oropharynx, hypopharynx and unspecified overlapping (Table 3). A positive association between BMI < 18.5 kg/m^2 at age 20 and the risk of unspecified or overlapping head and neck cancer was observed (Table 3). BMI loss from age 20 to 5 years prior to the interview time remained positively associated with hypopharyngeal and laryngeal cancer (Table 3).

When stratified by age, the results for younger and older groups were similar for BMI at interview (Supplemental Table S1). We further stratified by sex and detected that the positive association between BMI at interview and HNC risk was stronger for males (OR = 9.26, 95% CI 1.95–43.99). However, women at age 20 with a low BMI (< 18.5 kg/m^2) had a high HNC risk (OR = 2.36, 95% CI 1.28–4.36) (Supplemental Table S1). No apparent associations were observed between fruit/vegetable intake and BMI at age 20 (Supplemental Table S2).

Ever smokers and both never and ever drinkers had a higher risk of HNC with low BMI (< 18.5 kg/m2) and a lower risk of HNC with being obese (≥ 30 kg/m2) (Table 4). The inverse associations between BMI 2 years and 5 years prior to the interview and HNC risk only were observed among ever smokers and ever drinkers. Higher risks for individuals who were underweight at age 20 were limited to never smokers and never drinkers.

The risk of HNC decreased by approximately 8% and 6% for every 5 kg/m^2 increase of BMI 5 years before interview among ever smokers and ever drinker, respectively (Table 5). Although height in quartiles was not associated with the risk of HNC, there was a 2% reduction in the risk of HNC with every 5 cm increase in height (Table 5). We detected an increased risk of HNC (OR = 4.70, 95% CI 1.33–16.58) for every 10% increase among never smokers for BMI change from age 20 to 5 years before interview (Table 5). For potential interactions between BMI and smoking/drinking, we estimated joint and component effects but did not detect any interactions.

Since some of the interviews took place 6 months after diagnosis and we had concerns on reverse causality, we restricted the analysis to individuals who were diagnosed within 1 month, and the results were consistent with our overall results. We observed similar levels of risk, for example, being underweight at age 20 was associated with an increased risk of HNC (OR = 1.51, 95%CI 1.01, 2.24 overall and OR = 1.63, 95% CI 1.06–2.51 for patients diagnosed within 1 month). Approximately 63.9% of HNC patients were diagnosed within 1 month.

4. Discussion

In this study, participants were recruited from eight different centers in one of the largest case-control studies on HNC that has been conducted in East Asia. Similar to previous studies [3,7,8,10–14], being obese at interview was associated with a decreased risk of head and neck cancer, and being underweight at interview was associated with an increased risk of head and neck cancer. The increased risks of HNC associated with a low BMI at interview may be due to reverse causality [8]. One possible explanation of the association is that right before diagnosis, individuals may get dysphagia (difficulty in swallowing) or odynophagia (painful swallowing) or may have a change in taste and appetite because of undiagnosed lesions in the head and neck, which may decrease the overall caloric intake and lead to weight loss [3]. In addition, we did not find this association for BMI 2 or 5 years before interview in our study. The INHANCE pooled study of HNC also did not find this association between BMI at 2–5 years before diagnosis and HNC risk [3]. We believe that BMI 2 and 5 years prior to interview may be less impacted by the disability or loss of appetite to eat caused by HNC or early symptoms of HNC.

However, being underweight at age 20 was also associated with a higher HNC risk, and early symptoms would not explain such observations. The association was detected among never cigarette smokers and never alcohol drinkers at age 20 in our analysis. A possible explanation for this association is that people who are underweight may also have lower levels of vitamins and other micronutrients, which are associated with increased risks of HNC [15–17]. However, we did not detect any associations between BMI and dietary vegetable and fruit intake in this study. The dietary vegetable and fruit intake was assessed for individuals at the time of interview in our study, thus we were unable to assess if they changed their dietary habits during their lifetime. Another possible explanation to this was that there has been major socioeconomic development in Asia over the last several decades. The majority of our study population were living on very low incomes at age 20. The GDP per capita in China was approximately 90 US dollars in 1960 compared to about 450 US dollars worldwide, 113 US dollars in China in 1970 compared to about 802 US dollars worldwide and 195 US dollars in China in 1980 compared to about 2,518 US dollars worldwide [18]. The percentage of being underweight among age 7–18 in 1985 was 31.3% in China [19]. Perhaps being underweight was a marker for low socioeconomic status, which has been associated with HNC in previous studies [20].

Similar to the association observed among never smokers, the higher risk of HNC among individuals who were underweight at age 20 was only observed among never drinkers. These results support the role of low BMI at age 20 in the HNC development via the SES pathway. In the INHANCE pooled analysis, it has been shown that the association with SES was stronger among never tobacco smokers and never alcohol drinkers [20]. Our results suggest that BMI decreasing from age 20 to 5 years before interview was associated with a higher HNC risk. However,

Table 5
BMI, height, BMI change (as continuous variables) and the risk of HNC by cigarette smoking and drinking status.

	All		Never smoker		Ever smoker		Never drinker		Ever drinker	
	OR[a]	95%CI	OR[b]	95%CI	OR[a]	95%CI	OR[c]	95%CI	OR[a]	95%CI
BMI at interview for every 5 kg/m^2 increase	0.92	(0.89,0.96)	0.99	(0.94,1.05)	0.85	(0.80,0.90)	0.96	(0.91,1.00)	0.86	(0.80,0.92)
P-value		< .0001		0.7357		< .0001		0.0529		< .0001
BMI 5 years before interview for every 5 kg/m^2 increase	0.98	(0.94,1.02)	1.05	(0.99,1.11)	0.92	(0.87,0.97)	1.01	(0.96,1.06)	0.94	(0.88,1.00)
P-value		0.3007		0.1114		0.0017		0.6377		0.0480
BMI at age 20 for every 5 kg/m^2 increase	1.01	(0.96,1.06)	0.97	(0.90,1.05)	1.02	(0.96,1.09)	0.97	(0.91,1.04)	1.06	(0.98,1.14)
P-value		0.7173		0.4237		0.4765		0.4065		0.1335
Height for every 5 cm increase	0.98	(0.96,1.00)	0.99	(0.96,1.02)	0.97	(0.94,1.00)	0.98	(0.96,1.01)	0.97	(0.93,1.00)
P-value		0.0340		0.4137		0.0322		0.1632		0.0820
BMI change from age 20 to 5 years before interview for every 10% increase	0.67	(0.30,1.53)	4.7	(1.33,16.58)	0.14	(0.05,0.44)	2.00	(0.70,5.76)	0.11	(0.03,0.43)
P-value		0.3457		0.0161		0.0007		0.1975		0.0019

[a] Adjusted for age, sex, ethnicity, education, center, daily cigarettes per day, cigarette years, alcohol drinks per week, alcohol years, betel quid chewed per day and betel years.
[b] Adjusted for age, sex, ethnicity, education, center, alcohol drinks per week, alcohol years, betel quid chewed per day and betel years.
[c] Adjusted for age, sex, ethnicity, education, center, daily cigarettes per day, cigarette years, betel quid chewed per day and betel years.

BMI gain showed no association with HNC. When the analysis was stratified by smoking status, BMI loss from age 20 to 5 years before interview was associated with a higher risk of HNC only among never smokers. Reverse causality is a possible explanation for this association, although for the HNC patients diagnosed at older ages, for example at age 60, we would not expect reverse causality to start at age 20.

We observed an inverse association between height and HNC risk (2% lower in risk per 5 cm height increase), which is consistent with previous investigations on adult height and HNC risk within the INHANCE consortium that reported a 9% and 14% reduction in the risk of HNC with every 10 cm increase in height among men and women [21]. In the INHANCE study, every 10 cm increase in height was also associated with a lower HNC risk in Japan, but this association was only observed in women [21]. One possible explanation for our results is the influence of childhood or adolescent nutrition status that might have influenced both adult height and cancer risk [21].

There are certain limitations in our study. First, there might be recall bias due to the nature of a case-control study, and the weight and height data are self-reported. However, individuals might not necessarily associate height or weight separately with the risk of HNC, thus recall bias might not be differential among the cancer cases and controls. Certainly for weight and height at age 20 for older individuals, recall error is possible, but we would not expect recall bias which would be differential recall for cases compared to controls. Secondly, there was limited statistical power in stratified analyses on various factors. Thirdly, data on human papilloma virus (HPV) infection were not available. We conducted stratified analysis by subsite since HPV is more strongly associated with oropharyngeal cancer, but the BMI results for oral cavity and oropharynx were similar to those for hypopharynx and larynx. In addition, there is no established association between HPV infection and BMI. Thus, we did not expect that HPV would act as a confounder in our study.

This is one of the few studies investigating BMI and HNC risk in an Asian population. Other strengths of our study include adjustment for betel quid chewing frequency and duration which are strong risk factors for HNC, especially for oral cavity cancer in Taiwan [22]. We also adjusted on other well-established risk factors, alcohol drinking and cigarette smoking. Finally, we had BMI information from different time points to investigate the impact of potential reverse causation where early signs of HNC might have impacted the patient's diet. BMI at age 20 enabled us to assess the BMI association without the potential influence of HNC symptoms prior to diagnosis.

In summary, our study provided evidence for an inverse association between BMI and HNC risk in an East Asian population. Being underweight at age 20 was associated with a higher HNC risk among never cigarette smokers and never alcohol drinkers, whereas being underweight at interview was associated with a much higher HNC risk among ever cigarette smokers and ever alcohol drinkers. Low BMI at a young age along with smoking and drinking may be factors that can be used to identify individuals at high risk for head and neck cancer in this population. Whether these results are specific to the generation of individuals in our study needs to be studied further. Future studies on anthropometric measures such as waist-to-hip circumference in an East Asian population may further elucidate the possible association.

Authorship contribution

Dr. Yuan-Chin Amy Lee, Dr. Paolo Boffetta, Dr. Zuo-Feng Zhang and Dr. Mia Hashibe coordinated and designed the study. Yuji Chen and Shuang Li analyzed data. Yuji Chen drafted the manuscript. Dr. Yuan-Chin Amy Lee and Dr. Mia Hashibe also contributed to the manuscript writing. Dr. Qian Li, Dr. Chien-Jen Chen, Dr. Wan-Lun Hsu, Dr. Pen-Jen Lou, Dr. Cairong Zhu, Dr. Jian Pan, Dr. Hongbing Shen, Dr. Hongxia Ma, Dr. Lin Cai, Dr. Baochang He, Dr. Yu Wang, Dr. Xiaoyan Zhou, Dr. Qinghai Ji, Dr. Baosen Zhou, Dr. Wei Wu, Dr. Jie Ma and Dr. Min Dai collected the data and read the manuscript drafts. Dr. Daisuke Kawakita revised the manuscript critically. All authors read the manuscript and approved of it.

Conflicts of interest

None.

Acknowledgments

This work was supported by the University of Utah School of Medicine, Department of Family and Preventive Medicine Marian Bishop Award, University of Utah Study Design and Biostatistics Center, with funding in part from the National Cancer Institute through Cancer Center Support P30 CA042014 awarded to Huntsman Cancer Institute, and the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant 8UL1TR000105 (formerly UL1RR025764).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.04.008.

References

[1] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (6) (2018) 394–424.

[2] J. Ferlay, M. Colombet, I. Soerjomataram, C. Mathers, D.M. Parkin, M. Pineros, A. Znaor, F. Bray, Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods, Int. J. Cancer (2018).

[3] M.M. Gaudet, A.F. Olshan, S.C. Chuang, J. Berthiller, Z.F. Zhang, J. Lissowska, D. Zaridze, D.M. Winn, Q. Wei, R. Talamini, N. Szeszenia-Dabrowska, E.M. Sturgis, S.M. Schwartz, P. Rudnai, J. Eluf-Neto, J. Muscat, H. Morgenstern, A. Menezes, E. Matos, A. Bucur, F. Levi, P. Lazarus, C. La Vecchia, S. Koifman, K. Kelsey, R. Herrero, R.B. Hayes, S. Franceschi, V. Wunsch-Filho, L. Fernandez, E. Fabianova, A.W. Daudt, L. Dal Maso, M.P. Curado, C. Chen, X. Castellsague, S. Benhamou, P. Boffetta, P. Brennan, M. Hashibe, Body mass index and risk of head and neck cancer in a pooled analysis of case-control studies in the International head and neck cancer epidemiology (INHANCE) consortium, Int. J. Epidemiol. 39 (4) (2010) 1091–1102.

[4] D.H. Maasland, P.A. van den Brandt, B. Kremer, L.J. Schouten, Body mass index and risk of subtypes of head-neck cancer: the Netherlands cohort study, Sci. Rep. 5 (2015) 17744.

[5] E.E. Vokes, N. Agrawal, T.Y. Seiwert, HPV-associated head and neck cancer, J. Natl. Cancer Inst. 107 (12) (2015) djv344.

[6] Global Adult Tobacco Survey (GATS): China Fact Sheet, (2010) (Accessed 11/19 2018), http://www.who.int.

[7] M.M. Gaudet, C.M. Kitahara, C.C. Newton, L. Bernstein, P. Reynolds, E. Weiderpass, A.R. Kreimer, G. Yang, H.O. Adami, M.C. Alavanja, L.E. Beane Freeman, H. Boeing, J. Buring, A. Chaturvedi, Y. Chen, A.A. D'Aloisio, M. Freedman, Y.T. Gao, J.M. Gaziano, G.G. Giles, N. Hakansson, W.Y. Huang, I.M. Lee, M.S. Linet, R.J. MacInnis, Y. Park, A. Prizment, M.P. Purdue, E. Riboli, K. Robien, D.P. Sandler, C. Schairer, H.D. Sesso, X.Ou Shu, E. White, A. Wolk, Y.B. Xiang, A. Zelenuich-Jacquotte, W. Zheng, A.V. Patel, P. Hartge, A. Berrington de Gonzalez, S.M. Gapstur, Anthropometry and head and neck cancer:a pooled analysis of cohort data, Int. J. Epidemiol. 44 (2) (2015) 673–681.

[8] S.L. Park, Y.C. Lee, M. Marron, A. Agudo, W. Ahrens, L. Barzan, V. Bencko, S. Benhamou, C. Bouchardy, C. Canova, X. Castellsague, D.I. Conway, C.M. Healy, I. Holcatova, K. Kjaerheim, P. Lagiou, R.J. Lowry, T.V. Macfarlane, G.J. Macfarlane, B.E. McCartan, P.A. McKinney, F. Merletti, H. Pohlabeln, L. Richiardi, L. Simonato, L. Sneddon, R. Talamini, D. Trichopoulos, A. Znaor, P. Brennan, M. Hashibe, The association between change in body mass index and upper aerodigestive tract cancers in the ARCAGE project: multicenter case-control study, Int. J. Cancer 128 (6) (2011) 1449–1461.

[9] J.L. Petrick, M.M. Gaudet, M.C. Weissler, W.K. Funkhouser, A.F. Olshan, Body mass index and risk of head and neck cancer by race: the carolina head and neck cancer epidemiology study, Ann. Epidemiol. 24 (2) (2014) 160–164 e1.

[10] L. Radoi, S. Paget-Bailly, D. Cyr, A. Papadopoulos, F. Guida, C. Tarnaud, G. Menvielle, A. Schmaus, S. Cenee, M. Carton, B. Lapotre-Ledoux, P. Delafosse, I. Stucker, D. Luce, Body mass index, body mass change, and risk of oral cavity cancer: results of a large population-based case-control study, the ICARE study, Cancer Causes Control 24 (7) (2013) 1437–1448.

[11] J.H. Lubin, M.M. Gaudet, A.F. Olshan, K. Kelsey, P. Boffetta, P. Brennan, X. Castellsague, C. Chen, M.P. Curado, L. Dal Maso, A.W. Daudt, E. Fabianova, L. Fernandez, V. Wunsch-Filho, S. Franceschi, R. Herrero, S. Koifman, C. La Vecchia, P. Lazarus, F. Levi, J. Lissowska, I.N. Mates, E. Matos, M. McClean, A. Menezes, H. Morgenstern, J. Muscat, J. Eluf Neto, M.P. Purdue, P. Rudnai, S.M. Schwartz,

O. Shangina, E.M. Sturgis, N. Szeszenia-Dabrowska, R. Talamini, Q. Wei, D. Winn, Z.F. Zhang, M. Hashibe, R.B. Hayes, Body mass index, cigarette smoking, and alcohol consumption and cancers of the oral cavity, pharynx, and larynx: modeling odds ratios in pooled case-control data, Am. J. Epidemiol. 171 (12) (2010) 1250–1261.

[12] S. Franceschi, L. Dal Maso, F. Levi, E. Conti, R. Talamini, C. La Vecchia, Leanness as early marker of cancer of the oral cavity and pharynx, Ann. Oncol. 12 (3) (2001) 331–336.

[13] A. Nieto, M.J. Sanchez, C. Martinez, X. Castellsague, M.J. Quintana, X. Bosch, M. Conde, N. Munoz, R. Herrero, S. Franceschi, Lifetime body mass index and risk of oral cavity and oropharyngeal cancer by smoking and drinking habits, Br. J. Cancer 89 (9) (2003) 1667–1671.

[14] G.C. Kabat, C.J. Chang, E.L. Wynder, The role of tobacco, alcohol use, and body mass index in oral and pharyngeal cancer, Int. J. Epidemiol. 23 (6) (1994) 1137–1144.

[15] V. Edefonti, M. Hashibe, M. Parpinel, F. Turati, D. Serraino, K. Matsuo, A.F. Olshan, J.P. Zevallos, D.M. Winn, K. Moysich, Z.F. Zhang, H. Morgenstern, F. Levi, K. Kelsey, M. McClean, C. Bosetti, C. Galeone, S. Schantz, G.P. Yu, P. Boffetta, Y.C. Amy Lee, S.C. Chuang, C. La Vecchia, A. Decarli, Natural vitamin C intake and the risk of head and neck cancer: a pooled analysis in the International head and neck cancer epidemiology consortium, Int. J. Cancer 137 (2) (2015) 448–462.

[16] V. Edefonti, M. Hashibe, M. Parpinel, M. Ferraroni, F. Turati, D. Serraino, K. Matsuo, A.F. Olshan, J.P. Zevallos, D.M. Winn, K. Moysich, Z.F. Zhang, H. Morgenstern, F. Levi, K. Kelsey, M. McClean, C. Bosetti, S. Schantz, G.P. Yu, P. Boffetta, S.C. Chuang, Y.C. A.L, C. La Vecchia, A. Decarli, Vitamin E intake from natural sources and head and neck cancer risk: a pooled analysis in the international head and neck cancer epidemiology consortium, Br. J. Cancer 113 (1) (2015) 182–192.

[17] S.C. Chuang, M. Jenab, J.E. Heck, C. Bosetti, R. Talamini, K. Matsuo, X. Castellsague, S. Franceschi, R. Herrero, D.M. Winn, C. La Vecchia, H. Morgenstern, Z.F. Zhang, F. Levi, L. Dal Maso, K. Kelsey, M.D. McClean, T. Vaughan, P. Lazarus, J. Muscat, H. Ramroth, C. Chen, S.M. Schwartz, J. Eluf-Neto, R.B. Hayes, M. Purdue, S. Boccia, G. Cadoni, D. Zaridze, S. Koifman, M.P. Curado, W. Ahrens, S. Benhamou, E. Matos, P. Lagiou, N. Szeszenia-Dabrowska, A.F. Olshan, L. Fernandez, A. Menezes, A. Agudo, A.W. Daudt, F. Merletti, G.J. Macfarlane, K. Kjaerheim, D. Mates, I. Holcatova, S. Schantz, G.P. Yu, L. Simonato, H. Brenner, H. Mueller, D.I. Conway, P. Thomson, E. Fabianova, A. Znaor, P. Rudnai, C.M. Healy, G. Ferro, P. Brennan, P. Boffetta, M. Hashibe, Diet and the risk of head and neck cancer: a pooled analysis in the INHANCE consortium, Cancer Causes Control 23 (1) (2012) 69–88.

[18] The World Bank. GDP per capita, (2019) (Accessed 03/16 2019), https://data.worldbank.org/indicator/NY.GDP.PCAP.CD?end=2017&start=1960.

[19] B. Dong, Z. Wang, Y. Song, H.J. Wang, J. Ma, Understanding trends in blood pressure and their associations with body mass index in Chinese children, from 1985 to 2010: a cross-sectional observational study, BMJ Open 5 (9) (2015) e009050.

[20] D.I. Conway, D.R. Brenner, A.D. McMahon, L.M. Macpherson, A. Agudo, W. Ahrens, C. Bosetti, H. Brenner, X. Castellsague, C. Chen, M.P. Curado, O.A. Curioni, L. Dal Maso, A.W. Daudt, J.F. de Gois Filho, G. D'Souza, V. Edefonti, E. Fabianova, L. Fernandez, S. Franceschi, M. Gillison, R.B. Hayes, C.M. Healy, R. Herrero, I. Holcatova, V. Jayaprakash, K. Kelsey, K. Kjaerheim, S. Koifman, C. La Vecchia, P. Lagiou, P. Lazarus, F. Levi, J. Lissowska, D. Luce, T.V. Macfarlane, D. Mates, E. Matos, M. McClean, A.M. Menezes, G. Menvielle, F. Merletti, H. Morgenstern, K. Moysich, H. Muller, J. Muscat, A.F. Olshan, M.P. Purdue, H. Ramroth, L. Richiardi, P. Rudnai, S. Schantz, S.M. Schwartz, O. Shangina, L. Simonato, E. Smith, I. Stucker, E.M. Sturgis, N. Szeszenia-Dabrowska, R. Talamini, P. Thomson, T.L. Vaughan, Q. Wei, D.M. Winn, V. Wunsch-Filho, G.P. Yu, Z.F. Zhang, T. Zheng, A. Znaor, P. Boffetta, S.C. Chuang, M. Ghodrat, Y.C. Amy Lee, M. Hashibe, P. Brennan, Estimating and explaining the effect of education and income on head and neck cancer risk: INHANCE consortium pooled analysis of 31 case-control studies from 27 countries, Int. J. Cancer 136 (5) (2015) 1125–1139.

[21] E. Leoncini, W. Ricciardi, G. Cadoni, D. Arzani, L. Petrelli, G. Paludetti, P. Brennan, D. Luce, I. Stucker, K. Matsuo, R. Talamini, C. La Vecchia, A.F. Olshan, D.M. Winn, R. Herrero, S. Franceschi, X. Castellsague, J. Muscat, H. Morgenstern, Z.F. Zhang, F. Levi, L. Dal Maso, K. Kelsey, M. McClean, T.L. Vaughan, P. Lazarus, M.P. Purdue, R.B. Hayes, C. Chen, S.M. Schwartz, O. Shangina, S. Koifman, W. Ahrens, E. Matos, P. Lagiou, J. Lissowska, N. Szeszenia-Dabrowska, L. Fernandez, A. Menezes, A. Agudo, A.W. Daudt, L. Richiardi, K. Kjaerheim, D. Mates, J. Betka, G.P. Yu, S. Schantz, L. Simonato, H. Brenner, D.I. Conway, T.V. Macfarlane, P. Thomson, E. Fabianova, A. Znaor, P. Rudnai, C. Healy, P. Boffetta, S.C. Chuang, Y.C. Lee, M. Hashibe, S. Boccia, Adult height and head and neck cancer: a pooled analysis within the INHANCE Consortium, Eur. J. Epidemiol. 29 (1) (2014) 35–48.

[22] Y.C. Chen, C.H. Cheng, Y.C. Wang, T.J. Wu, H.S. Chou, K.M. Chan, W.C. Lee, C.F. Lee, R.S. Soong, Betel quid chewing leads to the development of unique de novo malignancies in liver transplant recipients, a retrospective single center study in Taiwan, Medicine 95 (37) (2016) e4901.