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## Anthropometry and head and neck cancer: a pooled analysis of cohort data

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## Abstract

**Background:** Associations between anthropometry and head and neck cancer (HNC) risk are inconsistent. We aimed to evaluate these associations while minimizing biases found in previous studies.

**Methods:** We pooled data from 1 941 300 participants, including 3760 cases, in 20 cohort studies and used multivariable-adjusted Cox proportional hazard regression models to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association of anthropometric measures with HNC risk overall and stratified by smoking status.

**Results:** Greater waist circumference (per 5 cm: HR = 1.04, 95% CI 1.03–1.05, *P*-value for trend = <0.0001) and waist-to-hip ratio (per 0.1 unit: HR = 1.07, 95% CI 1.05–1.09, *P*-value for trend = <0.0001), adjusted for body mass index (BMI), were associated with higher risk and did not vary by smoking status (*P*-value for heterogeneity = 0.85 and 0.44, respectively). Associations with BMI (*P*-value for interaction = <0.0001) varied by smoking status. Larger BMI was associated with higher HNC risk in never smokers (per 5 kg/m<sup>2</sup>: HR = 1.15, 95% CI 1.06–1.24, *P*-value for trend = 0.0006), but not in former smokers (per 5 kg/m<sup>2</sup>: HR = 0.99, 95% CI 0.93–1.06, *P*-value for trend = 0.79) or current smokers (per 5 kg/m<sup>2</sup>: HR = 0.76, 95% CI 0.71–0.82, *P*-value for trend = <0.0001). Larger hip circumference was not associated with a higher HNC risk. Greater height (per 5 cm) was associated with higher risk of HNC in never and former smokers, but not in current smokers.

**Conclusions:** Waist circumference and waist-to-hip ratio were associated positively with HNC risk regardless of smoking status, whereas a positive association with BMI was only found in never smokers.

**Key words:** Head and neck neoplasms, obesity, smoking, waist-hip ratio, waist circumference

### Key Messages

- In a pooled analysis of 1.9 million people, greater waist circumference and waist-to-hip ratio, adjusted for BMI, were associated with higher risk of squamous cell carcinoma of the head and neck and this did not vary by smoking status.
- Larger BMI was associated with higher HNC risk in never smokers, but not in former smokers or current smokers.
- Hip circumference was not associated with risk.
- Taller height was associated with higher risk of HNC in never and former smokers.

## Introduction

Cancers of the oral cavity, pharynx and larynx [referred to collectively as head and neck cancer (HNC)] diagnosed in Europe and North America are due primarily to tobacco

smoke and alcohol consumption.<sup>1</sup> However, there is growing evidence that other factors such as human papilloma virus infection and perhaps anthropometric factors might be associated with risk.<sup>1</sup>

In a large pooled analysis of 17 case-control HNC studies [International Head and Neck Cancer Epidemiology (INHANCE) Consortium], high body mass index (BMI) (i.e.  $\text{BMI} > 25.0 \text{ kg/m}^2$ ) was associated with lower risk of HNC, whereas low BMI (i.e.  $< 18.5 \text{ kg/m}^2$ ) was associated with higher risk, compared with BMI  $18.5\text{--}25.0 \text{ kg/m}^2$ . The elevated risk of HNC associated with low BMI persisted for both cigarette smokers/alcohol drinkers and non-smokers/non-drinkers; however, the reduced risk associated with high BMI was limited only to smokers/drinkers.<sup>2</sup> Although the large sample sizes included in this pooled analysis allowed for stratification by smoking status, it is possible that the inverse association between BMI and risk of HNC might be due to reverse causality as a result of decreases in BMI secondary to pre-malignant lesions/conditions, or to selection bias as a result of BMI-related effects on survival (i.e. heavier cases died earlier than normal-weight cases). In addition, in the INHANCE consortia,<sup>3</sup> there was an inverse association between height (per 10 cm) and risk of HNC. Whether possible selection bias, especially in the hospital-based case-control studies, could explain this inverse association is unclear, given that there was no association in the population-based case-control studies.

Results on the association between BMI and HNC incidence have been published from three large prospective cohort studies: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial;<sup>4</sup> the Cancer Prevention Study-II (CPS-II) Nutrition Cohort;<sup>5</sup> and the National Cancer Institute-American Association for Retired Persons (NCI-AARP) Diet and Health Study.<sup>6</sup> Estimates from PLCO<sup>4</sup> and CPS-II<sup>5</sup> were based on small numbers of cases (170 and 340 cases, respectively) and were null. Authors from the much larger NCI-AARP cohort (779 cases) reported an inverse association for BMI that was limited to current smokers, and positive associations for waist-to-hip ratio regardless of smoking status.<sup>6</sup>

To further evaluate the relationship between BMI and HNC, we conducted a pooled analysis of available cohort studies with body size data collected prior to cancer diagnosis. The large sample size afforded by pooling 20 cohort studies provided a sufficient number of cases to stratify by smoking history, thereby eliminating residual confounding due to cigarette smoking. Limiting the study design to only cohort studies minimized bias due to case selection and to weight loss secondary to disease progression prior to clinical diagnosis. Because assessing causal associations with BMI is biased in smokers,<sup>7</sup> and because of the availability of other anthropometric variables, we also examined associations of HNC risk with height, waist and hip circumferences and waist-to-hip ratio.

## Methods

### Study population

Member studies of the NCI Cohort Consortium with anthropometric data were invited to participate, and 20 cohorts (listed in [Supplementary Table 1](#), available as [Supplementary data](#) at *IJE* online) were included in this analysis. Written informed consent was obtained from study participants at entry into each of the respective cohorts or was implied by participants' return of the enrolment questionnaire. The present investigation was approved by the Institutional Review Board (IRB) at each participating institution or was considered within the scope of the originally approved IRB protocol.

Collaborators provided individual-level data for 2 277 220 men and women. Subjects were excluded if they were  $< 18$  or  $> 85$  years of age at the time of enrolment ( $n = 5507$ ), had  $< 1$  year of follow-up ( $n = 51 620$ ), were missing weight, height or BMI ( $n = 175 528$ ), had extreme values for BMI  $< 15$  or  $60 + \text{kg/m}^2$ ;  $n = 2172$ ) or height  $< 122$  or  $> 244$  cm;  $n = 139$ ), or had a history of cancer at baseline ( $n = 100 954$ ). Final analyses were based on a pooled cohort of 1 941 300 study subjects with baseline data.

### Exposure information

For participants in each cohort, de-identified data on anthropometry, smoking, alcohol, gender, age, education and other characteristics were provided. Weight and height were self-reported on the baseline survey for all cohorts with the exception of the MCCS and SISTERS cohorts (see [Supplementary Table 1](#) for study acronyms), in which they were measured by trained interviewers.<sup>8</sup> BMI was calculated as weight (in kg) divided by height (in m) squared, and categorized a priori. Young adult BMI (based on recalled weight at ages 18–21 years, depending on the cohort) was provided by 10 cohorts (AARP, AHS, COSM, CPS-II, IWHS, MCCS, PLCO, SMC, VITAL and WLH). Waist circumference was measured by the study participant for the IWHS, CPS-II, WLH and CTS cohorts, and by a trained interviewer for the MCCS, NYUWHS, SISTERS, SMHS and SWHS cohorts. Waist circumference was available from the baseline survey from COSM, IWHS, MCCS, SISTERS, SMC, SMHS, SWHS and WLH cohorts, from subsequent surveys 1 to 8 years later from AARP, BCDDP, CPS-II, CTS, EPIC and NYUWHS cohorts. The same studies had hip circumference data with the exception of the CPS-II cohort. Waist-to-hip ratio was calculated by dividing waist circumference (in cm) by hip circumference (in cm). Circumference variables were categorized using predefined, sex-specific cut-points. Anthropometric and

covariate data from each of the cohorts were harmonized using standard definitions and categories across studies, and then combined for analysis.

### Case ascertainment

Cases were ascertained through self-report, state cancer registries and/or medical record review. Cases were defined as squamous cell carcinoma of the head and neck. Lip cancer was excluded. Subsites were considered: oral cavity cancer was defined as ICD-O/10 codes (C02.0–02.3, 03.0, 03.1, 03.9, 04.0, 04.1, 04.8, 04.9, 05.0, 06.0–06.2, 06.8, 06.9) or ICD-9 (141.1–141.5, 143.0, 143.1, 143.8, 143.9, 144.0, 144.1, 144.8, 144.9, 145.0–145.2, 145.6, 145.8, 145.9); oropharynx cancer was defined as ICD-O/10 codes (C01.9, 02.4, 05.1, 05.2, 09.0, 09.1, 09.8, 09.9, 10.0–10.4, 10.8, 10.9) or ICD-9 (141.0, 141.6, 145.3, 145.4, 146.1, 146.2); hypopharynx cancer was defined as ICD-O/10 codes (C12, 13.0–13.2, 13.8, 13.9) or ICD-9 (148.0–148.3, 148.8, 148.9); oral/pharynx cancer not otherwise specified was defined as ICD-O/10 codes (C02.8, 02.9, 05.8, 05.9, 14.0, 14.2, 14.8) or ICD-9 (141.8, 141.9, 145.5, 149.0, 149.1, 149.8, 149.9); and larynx cancer was defined as ICD-O/10 codes (C32.0–32.3, 32.8, 32.9) or ICD-9 (161.0–161.3, 161.8, 161.9). Each cohort provided 15 to 1573 cases of squamous cell carcinoma of the HNC (Supplementary Table 1). Analyses were based on a total of 3760 cases.

### Statistical analyses

Person-time was calculated from the date of the return of the survey that included the anthropometric variable of interest (usually baseline questionnaire for BMI and a subsequent follow-up questionnaire for waist and hip circumference) until the date of the first-occurring event: cancer diagnosis, death, withdrawal from study, loss to follow-up or administrative end of cohort-specific follow-up time. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using Cox proportional hazards regression models that were age-adjusted and multivariable-adjusted. All proportional hazards models were adjusted for age using the stratified Cox procedure with 1-year age strata.<sup>9</sup> Multivariable-adjusted models included cohort, sex, genetic ancestry (African, Asian, European, other/unknown), education (college graduate or more, some college, high school graduate, less than a high school education, missing), alcohol intake at baseline (non-drinker, deciles of grams of alcohol per day, missing, unknown), and cigarette smoking status at baseline (non-smoker, current smoker, former smoker, ever smoker/unclassifiable, missing). Associations of waist circumference, hip circumference and waist-to-hip ratio with HNC were examined with and without

adjustment for baseline BMI. Associations of each of the anthropometric variables were examined in sensitivity analyses adjusted for height. The proportional hazards assumption was assessed using an interaction term with continuous exposure and time. No violations were observed with the exception of height overall ( $P = 0.013$ ); however, upon visual inspection, the log-log survivor curves for height crossed only in the first 2 years of follow-up time, which was statistically detectable due to the large sample size.

Each of the anthropometric variables was modelled as continuous and categorical variables. The  $P$ -value for linear trend was calculated from the continuous variable; for BMI, the underweight group (BMI 15.0–18.4 kg/m<sup>2</sup>) was excluded. Because the NIH-AARP cohort was the largest study (Supplementary Table 1), we excluded it in sensitivity analyses.

Effect modification was evaluated by comparing the  $-2$  log likelihood estimates of models with and without the interaction term(s). We stratified anthropometric variables and HNC risk jointly by smoking and alcohol drinking status and found no difference in associations ( $P$  for interaction  $>0.05$ ); therefore, we present results stratified only by smoking status. We further examined residual confounding in analyses stratified by cigarettes per day (CPD) in current smokers and years since quit in former smokers. Effect modification was assessed for the following variables: age at baseline ( $<65$ ,  $65+$  years), sex (male, female), genetic ancestry (African, European, other/unknown), region (North America, Europe, Asia, Australia/New Zealand) and waist circumference (lower category: men  $<100$  cm and women  $<80$  cm, higher category: men  $100+$  cm and women  $80+$  cm). Case heterogeneity by anatomical sub-site of the HNC tumour [oral cavity, hypopharynx, oropharynx, oro/hypopharynx not otherwise specified (NOS), larynx] also was evaluated. Differences in results among never smokers across cohorts were evaluated by forest plots and by comparing the associations using the  $I^2$  index, which indicates the percentage of total variation across studies that is due to heterogeneity rather than chance.<sup>10</sup> To evaluate a possible bias due to weight loss secondary to disease progression prior to diagnosis, we excluded the first 2 years of follow-up time in sensitivity analyses, and results were nearly identical to those presented.

All analyses were conducted using SAS statistical software, version 9.3 (SAS Institute).

## Results

Covariates and anthropometric variables varied by baseline smoking status and sex (Table 1). Current smokers were more likely to be younger at baseline, less educated, alcohol drinkers, thinner and with smaller hips than never smokers in both men and women.

**Table 1.** Description of study population by sex and smoking status at baseline

		Smoking status at baseline							
		Men				Women			
		Never (%)	Former (%)	Current (%)	Unknown (%)	Never (%)	Former (%)	Current (%)	Unknown (%)
Total N		265608	363394	146421	16304	661046	322700	148446	17381
Age at baseline (years)	<40	4.8	1.1	3.8	2.8	9.2	6.8	12.2	5.7
	40–<50	12.3	6.8	24.4	6.7	21.6	15.9	20.1	15.1
	50–<60	35.5	33.4	39.6	32.0	32.0	35.5	37.9	33.4
	60–<70	39.3	50.2	27.6	52.0	30.7	35.1	26.6	38.9
	70+	8.0	8.5	4.7	6.5	6.5	6.6	3.2	7.0
Genetic ancestry	European	87.8	93.1	76.3	86.3	83.5	94.7	94.0	81.7
	African	1.5	1.7	1.9	3.0	2.3	2.6	2.7	4.5
	Asian	8.8	3.2	20.4	1.0	12.2	0.9	1.8	1.0
	Other/ unknown	1.9	2.0	1.4	9.7	2.0	1.8	1.5	12.9
Educational attainment	<High school graduate	14.1	15.6	31.8	12.7	21.5	12.0	24.4	11.0
	High school graduate	14.8	16.3	20.1	15.1	20.1	17.7	20.8	19.7
	Some college	20.9	28.1	24.2	22.6	23.2	30.1	29.7	19.6
	College graduate or higher	48.3	37.7	22.0	31.0	32.8	37.0	22.3	27.5
	Unknown	1.9	2.2	1.9	18.6	2.5	3.2	2.8	22.1
Alcohol intake	Unknown	12.2	10.0	7.1	10.3	5.7	6.4	4.9	17.5
	No use	23.5	15.7	22.1	19.0	39.0	19.3	21.7	24.8
	<1 drink/ day	44.4	42.6	32.9	45.0	47.9	58.1	54.0	47.3
	1–<2 drinks/ day	11.2	15.0	14.9	11.8	5.3	10.4	10.7	6.4
	2+ drinks/ day	8.7	16.7	23.1	13.8	2.2	5.8	8.6	4.0
Height (cm)	M < 170, W < 160	15.3	12.5	21.8	14.1	32.8	23.2	27.3	29.3
	M 170–<175, W 160–<165	20.5	19.9	23.8	20.7	28.6	28.7	28.9	29.4
	M 175–<180, W 165–<170	26.5	27.5	24.7	27.0	23.2	27.5	25.9	24.6
	M 180+, W 170+	37.7	40.1	29.6	38.2	15.4	20.6	17.9	16.7
	Unknown	0.6	0.4	1.7	0.5	1.8	1.3	2.8	1.7
Body mass index (kg/m <sup>2</sup> )	15.0–18.4	0.6	0.4	1.7	0.5	1.8	1.3	2.8	1.7
	18.5–<25	37.5	28.7	43.8	29.5	49.7	49.9	55.3	49.6
	25–<30	46.7	50.3	41.9	49.3	31.1	30.6	29.1	30.3
	30+	15.3	20.6	12.6	20.7	17.4	18.1	12.7	18.4
	Unknown	47.0	46.7	33.3	49.9	33.6	41.3	35.7	39.2
Waist circumference (cm)	M < 90, W < 70	18.5	13.0	28.0	13.1	11.7	9.4	12.1	11.8
	M 90–<100, W 70–<80	20.7	21.1	22.7	20.1	22.5	20.0	22.3	20.2
	M 100–<110, W 80–<90	9.9	13.1	11.4	11.6	17.9	15.4	17.0	15.3
	M 110+, W 90+	4.0	6.1	4.6	5.3	14.2	13.9	12.8	13.5
	Unknown	55.8	56.6	38.5	55.3	39.2	48.1	39.6	44.0
Hip circumference (cm)	M < 95, W < 90	9.5	6.7	19.7	7.3	8.1	4.9	9.3	6.7
	M 95–<105, W 90–<100	23.3	22.2	29.8	22.9	23.6	20.1	24.6	20.3
	M 105–<115, W 100–<110	9.4	11.6	10.0	11.4	19.3	17.4	18.5	18.1
	M 115+, W 110+	2.0	2.9	2.0	3.1	9.9	9.5	8.0	10.9
	Unknown	55.9	56.7	38.7	55.5	39.3	48.2	39.7	44.2
Waist-to-hip ratio	M < 0.90, W < 0.75	13.9	10.0	18.9	11.1	14.1	13.4	12.8	16.4
	M 0.90–<0.95, W 0.75–<0.8	15.1	14.1	19.3	14.4	17.5	15.0	17.2	16.0
	M 0.95–<1.00, W 0.80–<0.8	9.3	10.6	13.2	10.2	15.3	11.7	14.8	11.8
	M 1.00+, W 0.85+	5.9	8.6	9.9	8.8	13.8	11.6	15.4	11.7
	Unknown								

M, men; W, women.

### Associations with height

Height was associated positively with HNC incidence overall; however, the associations varied by smoking status ( $P$ -value for interaction = 0.04). Greater height was associated with higher HNC risk in never and former smokers, but was associated with lower risk in current smokers (Table 2). Results were consistent across studies ( $I^2 = 0\%$ ).

### Associations with waist circumference and waist-to-hip ratio

Greater waist circumference (per 5 cm: HR = 1.04, 95% CI 1.03–1.05,  $P$ -value for trend = <0.0001) and waist-to-hip ratio (per 0.1 unit: HR = 1.07, 95% CI 1.05–1.09,  $P$ -value for trend = <0.0001), adjusted for BMI, were associated with higher risk in all participants and did not vary

by smoking status ( $P$ -value for heterogeneity = 0.85 and 0.44, respectively). We found moderate heterogeneity across studies for waist circumference ( $I^2 = 46.4\%$ ), but similar study-specific associations with waist-to-hip ratio ( $I^2 = 0\%$ ). The association of HNC risk with waist circumference or waist-to-hip ratio did not change after controlling for height (data not shown).

### Associations with body mass index

BMI was associated inversely with HNC overall with no evidence of between-study heterogeneity ( $I^2 = 0\%$ ; [Supplementary Figure 1](#), available as [Supplementary data](#) at *IJE* online). However, the association differed by smoking status ( $P$  for interaction by smoking status =  $<0.0001$ ) with a positive association between BMI and HNC in never smokers, no association in former smokers and an inverse association in current smokers. HRs were similar after further control for smoking duration and cigarettes per day (data not shown). Because analyses of waist and hip circumferences were restricted to a subset of studies, we also examined the association between BMI and HNC in this subset (data not shown) and did not observe any meaningful differences from those shown in [Table 2](#). Controlling for waist circumference changed the interpretation of the BMI results: the HR per  $5 \text{ kg/m}^2$  in never smokers went from 1.14 to 1.01 (95% CI 0.86–1.18), in former smokers from HR = 1.01 to HR = 0.84 (95% CI 0.73–0.97) and in current smokers from HR = 0.77 to HR = 0.62 (95% CI 0.53–0.73). Controlling for height, hip circumference and waist-to-hip ratio did not meaningfully change the interpretation of the BMI results with the exception of the model controlling waist-to-hip ratio in current smokers (the HR per  $5 \text{ kg/m}^2$  went from 0.77 to 0.67 (95% CI 0.59–0.76) (data not otherwise shown). Young adult BMI was not associated with HNC risk in never, former or current smokers ( $P$  for trend  $> 0.57$ ; data not shown).

### Effect modification

Further stratification on alcohol intake and smoking status (data not shown) did not show any differences in associations as compared with those stratified by smoking alone. Removing the NIH-AARP cohort in sensitivity analyses only changed the hundredths place of the associations with the continuous anthropometry variables (data not shown).

In current smokers ([Table 3](#)), the inverse association between BMI and risk of HNC was stronger in heavy smokers compared with light smokers ( $P$ -value for interaction = 0.06). Waist circumference was associated inversely with risk for the heaviest smokers, but was not associated with risk for the lightest smokers ( $P$ -value for

interaction = 0.01). Associations of waist-to-hip ratio with HNC risk also varied by CPD ( $P$ -value for interaction = 0.01). The associations of height and hip circumference with HNC risk did not differ by CPD ( $P$ -value for interaction = 0.76 and 0.26, respectively).

In former smokers ([Table 3](#)), the association between BMI and HNC varied by categories of years since quitting ( $P$  for interaction = 0.006) with an inverse association among participants who quit within 10 years of enrolling in the cohort, and a positive association among long-term quitters.

In never smokers, the associations of height, waist and hip circumferences and waist-to-hip ratio with the risk of HNC stratified by subsite were similar ( $P$ -value for site-heterogeneity  $> 0.09$ ; [Supplementary Table 2](#), available as [Supplementary data](#) at *IJE* online). However, BMI was associated positively with oral/pharynx NOS and larynx but not with other sites ( $P$ -value for site-heterogeneity = 0.01). For the association between BMI and HNC risk, there was no evidence of effect modification by age, sex, genetic ancestry, geographical region or waist circumference in all subjects ( $P$  for interaction  $\geq 0.12$ ), nor in never smokers ( $P$  for interaction  $\geq 0.53$ ; data not otherwise shown).

### Discussion

In our large pooled analysis of 1.9 million people including 3760 HNC cases, greater waist circumference and waist-to-hip ratio, adjusted for BMI, were associated with higher risk and did not vary by smoking status. Associations with BMI and hip circumference varied by smoking status. Larger BMI was associated with higher HNC risk in never smokers, but not in former smokers or current smokers. Larger hip circumference was not associated with a higher HNC risk. Taller height was associated with higher risk of HNC in never and former smokers. Associations in never smokers were in the positive direction for all anthropometry measures.

The different patterns of results for the anthropometric factors by smoking status in our study suggest that the overall associations of HNC are strongly confounded by smoking characteristics. Because smoking is a strong risk factor for HNC and is associated with lower weight, confounding by smoking is best modelled by stratification<sup>11</sup> and, in particular, evaluated separately among never smokers.<sup>12</sup> In our study, we found a positive association between BMI and HNC risk in never smokers and an inverse association in current smokers. Furthermore, the confounding effect of smoking on the BMI association was also evident in the pattern of results by smoking intensity in current smokers and years since quitting in former smokers. Based on our findings, associations with waist

**Table 2.** Multivariable-adjusted<sup>a</sup> hazard ratios (HR) and 95% confidence intervals (CI) for the associations of measures of body size with risk of head and neck cancer, overall and by smoking status

Exposure	Category	All		Never smoker		Former smoker		Current smoker		P for interaction by smoking status
		Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	
Height (cm)	M < 170, W < 160	653	1.00 (ref)	167	1.00 (ref)	196	1.00 (ref)	280	1.00 (ref)	0.043
	M 170–<175, W 160–<165	858	1.04 (0.94–1.16)	202	1.22 (0.99–1.51)	308	1.03 (0.86–1.23)	330	0.96 (0.81–1.13)	
	M 175–<180, W 165–<170	995	1.03 (0.93–1.15)	198	1.19 (0.95–1.48)	395	1.02 (0.85–1.22)	380	0.97 (0.82–1.13)	
	M 180+, W 170+	1254	1.09 (0.98–1.21)	229	1.32 (1.05–1.66)	609	1.20 (1.01–1.43)	377	0.83 (0.70–0.98)	
	per 5 cm		1.02 (1.00–1.05)		1.08 (1.02–1.13)		1.05 (1.01–1.09)		0.95 (0.91–0.99)	
	P for trend		0.07		0.005		0.008		0.01	
Body mass index (kg/m <sup>2</sup> )	15.0–<21	354	1.28 (1.11–1.46)	63	1.17 (0.85–1.61)	78	1.24 (0.94–1.63)	208	1.30 (1.08–1.57)	<0.0001
	21–<23	509	1.00 (ref)	100	1.00 (ref)	150	1.00 (ref)	247	1.00 (ref)	
	23–<25	704	0.87 (0.78–0.98)	145	1.00 (0.77–1.29)	257	0.92 (0.75–1.13)	284	0.80 (0.68–0.95)	
	25–<30	1586	0.89 (0.81–0.99)	333	1.20 (0.95–1.50)	726	1.01 (0.84–1.21)	488	0.71 (0.61–0.83)	
	30+	607	0.85 (0.76–0.96)	155	1.40 (1.08–1.81)	297	0.96 (0.79–1.18)	140	0.58 (0.47–0.72)	
	Per 5 kg/m <sup>2</sup>		0.94 (0.90–0.98)		1.15 (1.06–1.24)		0.99 (0.93–1.06)		0.76 (0.71–0.82)	
	P for trend <sup>b</sup>		0.003		0.0006		0.79		<0.0001	
Waist circumference (cm)	M < 90, W < 70	484	1.00 (ref)	91	1.00 (ref)	137	1.00 (ref)	249	1.00 (ref)	0.85
	M 90–<100, W 70–<80	612	0.82 (0.72–0.93)	137	1.03 (0.78–1.36)	222	0.83 (0.67–1.03)	237	0.74 (0.62–0.89)	
	M 100–<110, W 80–<90	515	1.01 (0.89–1.16)	119	1.25 (0.93–1.68)	215	1.15 (0.92–1.43)	173	0.86 (0.70–1.05)	
	M 110+, W 90+	320	1.08 (0.93–1.25)	94	1.51 (1.09–2.08)	132	1.21 (0.94–1.55)	86	0.80 (0.62–1.04)	
	per 5 cm		1.02 (1.00–1.04)		1.06 (1.02–1.10)		1.03 (1.00–1.07)		0.98 (0.95–1.01)	
	P for trend		0.10		0.007		0.06		0.18	
	Per 5 cm controlling for BMI		1.04 (1.03–1.05)		1.07 (1.01–1.14)		1.06 (1.01–1.11)		1.04 (1.02–1.05)	
	P for trend		<0.0001		0.022		0.01		<0.0001	
Hip circumference (cm)	M < 95, W < 90	381	1.00 (ref)	87	1.00 (ref)	79	1.00 (ref)	211	1.00 (ref)	0.0025
	M 95–<105, W 90–<100	710	0.79 (0.69–0.91)	130	0.73 (0.53–1.00)	256	1.07 (0.81–1.40)	309	0.72 (0.60–0.87)	
	M 105–<115, W 100–<110	445	0.84 (0.72–0.97)	109	0.89 (0.64–1.26)	188	1.20 (0.90–1.59)	137	0.65 (0.52–0.82)	
	M 115+, W 110+	145	0.77 (0.63–0.95)	56	1.10 (0.73–1.63)	57	1.01 (0.70–1.45)	28	0.46 (0.31–0.69)	
	Per 5 cm		0.97 (0.94–0.99)		1.03 (1.00–1.07)		1.00 (0.96–1.04)		0.89 (0.85–0.93)	
	P for trend		0.02		0.04		0.90		<0.0001	
	Per 5 cm controlling for BMI		0.99 (0.95–1.02)		1.03 (0.99–1.07)		0.99 (0.94–1.05)		0.93 (0.88–0.99)	
	P for trend		0.42		0.18		0.77		0.02	
Waist-to-hip ratio	M < 0.90, W < 0.75	311	1.00 (ref)	73	1.00 (ref)	113	1.00 (ref)	120	1.00 (ref)	0.44
	M 0.90–<0.95, W 0.75–<0.80	480	1.03 (0.89–1.19)	100	0.99 (0.73–1.34)	163	0.90 (0.71–1.14)	204	1.16 (0.92–1.45)	
	M 0.95–<1.00, W 0.80–<0.85	410	1.06 (0.91–1.23)	109	1.27 (0.94–1.73)	127	0.86 (0.66–1.11)	166	1.12 (0.89–1.43)	
	M 1.00+, W 0.85+	476	1.30 (1.12–1.50)	100	1.23 (0.89–1.69)	174	1.25 (0.98–1.59)	195	1.38 (1.09–1.75)	
	Per 0.1 unit		1.06 (1.04–1.09)		1.08 (0.96–1.22)		1.10 (1.01–1.20)		1.06 (1.02–1.10)	
	P for trend		<0.0001		0.2013		0.0351		0.0017	
	Per 0.1 controlling for BMI		1.07 (1.05–1.09)		1.06 (0.93–1.11)		1.10 (1.01–1.21)		1.08 (1.04–1.12)	
	P for trend		<0.0001		0.36		0.03		0.0001	

M, men; W, women.

<sup>a</sup>Multivariable-adjusted models adjusted for age, sex, genetic ancestry, cohort, education, alcohol drinking status, and smoking status.

<sup>b</sup>The P-value for linear trend was calculated excluding the underweight category.

circumference and waist-to-hip ratio might be independent of smoking status because the associations with HNC were almost all in the positive direction in never, former and current smokers. However, the association with waist circumference in current smokers was in the positive direction only after including BMI in the model.

Our results are consistent with the dual effect that cigarette smoking has on body habitus.<sup>7</sup> Smoking is associated with lower weight through nicotine's effects on acute increases in metabolic energy expenditure,<sup>13</sup> decreases in calorie absorption and appetite suppression.<sup>14</sup> However, heavy smokers tend to weigh more than light smokers,<sup>15–17</sup> and smoking is associated with central obesity and insulin resistance.<sup>18</sup> During a 3-year interval of a long-term longitudinal study of 1122 men aged 19 to

102 years, waist-to-hip ratio increased more among smokers who continued to smoke than among smokers who quit, and more among non-smokers who became smokers than among non-smokers who remained non-smokers; these changes were not explained by changes in weight or physical activity.<sup>19</sup> Systemic consequences of obesity development among smokers have been well studied and include elevated levels of sex steroid hormones, cortisol, insulin/insulin-like growth factors, glucose and inflammatory markers and reduced levels of adiponectin;<sup>20–22</sup> however, in the head and neck tissue, the biological mechanisms for overall or centralized obesity and carcinogenesis are unclear. Further knowledge about the biological mechanisms mediating this association might aid in the identification of people at highest risk of HNC.

**Table 3.** Multivariable-adjusted<sup>a</sup> hazard ratios (HR) and 95% confidence intervals (CI) for the associations of measures of body size with risk of head and neck cancer by cigarettes per day (CPD) in current smokers and years since quitting in former smokers

	Height (per 5 cm) HR (95% CI) P for trend	Body mass index (per 5 kg/m <sup>2</sup> ) HR (95% CI) P for trend <sup>b</sup>	Waist circumference (per 5 cm) HR (95% CI) P for trend	Hip circumference (per 5 cm) HR (95% CI) P for trend	Waist-to-hip ratio (per 0.1 unit) HR (95% CI) P for trend
Cigarettes per day (CPD) in current smokers					
<20	0.94 (0.82–1.07) 0.32	0.79 (0.61–1.03) 0.079	0.99 (0.90–1.08) 0.82	0.87 (0.77–0.99) 0.031	1.30 (1.00–1.70) 0.054
20–<30	0.98 (0.86–1.11) 0.69	0.72 (0.56–0.92) 0.0085	0.99 (0.91–1.07) 0.76	0.82 (0.73–0.92) 0.0008	1.43 (1.16–1.76) 0.0009
≥ 30	1.04 (0.89–1.23) 0.60	0.61 (0.44–0.84) 0.0025	0.90 (0.81–1.00) 0.060	0.79 (0.69–0.91) 0.0010	1.07 (0.78–1.46) 0.67
P-value for interaction	0.76	0.06	0.01	0.26	0.01
Years since quitting in former smokers					
<10	1.02 (0.96–1.09) 0.46	0.82 (0.73–0.92) 0.0006	0.98 (0.93–1.04) 0.57	0.92 (0.86–0.99) 0.032	1.09 (0.94–1.27) 0.23
10–<20	1.13 (1.02–1.26) 0.025	0.93 (0.77–1.12) 0.44	1.01 (0.92–1.10) 0.86	1.01 (0.88–1.15) 0.93	1.09 (0.80–1.47) 0.60
20+	1.00 (0.89–1.12) 0.99	1.15 (0.96–1.37) 0.13	1.09 (0.99–1.19) 0.073	1.12 (0.97–1.30) 0.12	1.11 (0.78–1.58) 0.56
P-value for interaction	0.77	0.006	0.20	0.10	0.83

<sup>a</sup>Multivariable-adjusted models included age, sex, genetic ancestry, cohort, education and alcohol drinking status.

<sup>b</sup>The P-value for linear trend was calculated excluding the underweight category.

In the only other prospective study to examine the association between height and HNC risk, the Million Women's Study,<sup>23</sup> the association with cancers of the mouth and pharynx was null, but based on smaller numbers of cases (351 cases in never smokers and 443 cases in current smokers) and the confidence intervals for never and current smokers included the summary estimates reported for height in our study. Together, the results of our large pooled analysis and the Million Women's Study do not rule out a possible direct association. The biological mechanisms underlying a possible positive association between height and HNC risk are unknown, but might be similar to other purported height-related mechanisms including higher levels of insulin-like growth factors.<sup>24, 25</sup>

The large number of cases of HNC provided substantial precision in estimating relative risks for six different anthropometric factors, even after stratifying by smoking status. Despite this large sample size, statistical power to detect possible differences by anatomical site in never smokers was still limited, especially for waist and hip circumferences that were available from fewer cohorts. The prospectively collected anthropometric data minimized the effect of weight loss due to pre-clinical disease and prevented recall bias suffered by retrospective studies that comprise much of the existing literature on this topic. The

multiple measures of body habitus allowed us to compare and contrast the effect of confounding by smoking and the associations with overall vs central adiposity.

In this large pooled analysis of prospective studies, BMI in never smokers, height in current and former smokers and waist circumference or waist-to-hip ratio regardless of smoking status were associated positively with risk of HNC. These data provide further evidence of the role of excess adiposity in carcinogenesis. Our results also indicate the importance of examining non-smoking risk factors for smoking-related cancers in never smokers.

## Supplementary Data

Supplementary data are available at *IJE* online.

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