Research Article

Cancer Epidemiology, Biomarkers & Prevention

Measured Adiposity in Relation to Head and Neck Cancer Risk in the European Prospective Investigation into Cancer and Nutrition

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Abstract

Background: Emerging evidence from cohort studies indicates that adiposity is associated with greater incidence of head and neck cancer. However, most studies have used self-reported anthropometry which is prone to error.

Methods: Among 363,094 participants in the European Prospective Investigation into Cancer and Nutrition study (EPIC) with measured anthropometry, there were 837 incident cases of head and neck cancer. Head and neck cancer risk was examined in relation to body mass index (BMI) [lean: <22.5 kg/m^2, normal weight (reference): 22.5–24.9 kg/m^2, overweight 25–29.9 kg/m^2, obese: ≥30 kg/m^2], waist circumference (WC), hip circumference (HC), and waist-to-hip ratio (WHR) using Cox proportional hazards models.

Results: Among men, a BMI < 22.5 kg/m^2 was associated with higher head and neck cancer risk [HR 1.62; 95% confidence interval (CI), 1.23–2.12)]; BMI was not associated with head and neck cancer among women. WC and WHR were associated with greater risk of head and neck cancer among women (WC per 5 cm: HR, 1.08; 95% CI, 1.02–1.15; WHR per 0.1 unit: HR, 1.64; 95% CI, 1.38–1.93). After stratification by smoking status, the association for WHR was present only among smokers ($P_{interaction} = 0.004$). Among men, WC and WHR were associated with head and neck cancer only upon additional adjustment for BMI (WC per 5 cm: HR 1.16; 95% CI, 1.07–1.26; WHR per 0.1 unit: HR, 1.42; 95% CI, 1.21–1.65).

Conclusions: Central adiposity, particularly among women, may have a stronger association with head and neck cancer risk than previously estimated.

Impact: Strategies to reduce obesity may beneficially impact head and neck cancer incidence. *Cancer Epidemiol Biomarkers Prev; 26(6); 895–904. ©2017 AACR.*

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Introduction

Cancers of the oral cavity, pharynx, and larynx (known collectively as head and neck cancers or head and neck cancer) are the sixth most common form of cancers worldwide (1). Head and neck cancer is positively associated with tobacco (2), alcohol (2), and human papillomavirus (HPV), especially HPV-16 (3). Evidence from case–control studies suggest that adiposity was inversely associated with the risk of head and neck cancer (4–12), an observation that was in contrast to the positive association with BMI for other cancer sites, such as breast, esophagus (adenocarcinoma), endometrium, and colon (13–16). Initial results from two prospective studies indicated that BMI classification was not associated with head and neck cancer risk (17, 18), but the number of cases in both studies ($n < 350$) limited the capacity for subgroup analysis. Subsequently, evidence of a divergent association for measures of anthropometry and head and neck cancer was reported by a large pooled consortium of twenty cohort studies (19): BMI was inversely associated with head and neck cancer risk among current smokers, whereas it was positively associated with head and neck cancer risk among nonsmokers. Furthermore, greater abdominal obesity (waist circumference or waist-to-hip ratio) was associated with higher head and neck cancer risk in the consortium study, regardless of smoking status (19). These results represent a substantial development in the characterization of anthropometry and head and neck cancer. However, the majority of studies in the pooled cohort relied on self-reported measures of anthropometry, which are prone to error (20–22). Greater precision in the estimates of the relationship between anthropometry and head and neck cancer could be gained through analysis of those with measured anthropometry.

The aim of the present analysis was to examine the association between measures of general adiposity (BMI), central adiposity (waist circumference, hip circumference, and waist-to-hip ratio) and head and neck cancer among participants in the European Prospective Investigation into Cancer and Nutrition (EPIC), further evaluating associations for differences by smoking status. Our analysis also incorporates information on changes in smoking status and weight after baseline, which (to the best of our knowledge) has not previously been included in analyses of anthropometry and head and neck cancer risk.

Materials and Methods

General study description

EPIC is a multicenter prospective cohort study, which recruited 521,448 volunteers from 23 centers in 10 countries (Denmark, France, Germany, Greece, Italy, Norway, the Netherlands, Spain, Sweden, and the United Kingdom) between 1992 and 2000. The study design and population has been described in detail previously (23, 24). In brief, the study included volunteers aged mostly 25 to 70 years at the time of recruitment. Questionnaires on diet, education, occupation, previous illnesses, alcohol, tobacco consumption, and physical activity were completed by participants. The study was approved by all relevant ethical review boards, and all participants provided consent for the retention of acquired data and follow-up for incidence of cancer and death.

Study sample

There were 491,992 eligible participants who had no history of prevalent cancer (except for nonmelanoma skin cancer) at baseline and complete information on length of follow-up. Participants were excluded if they had missing measurements of height or weight, waist circumference (WC, centimeters) and hip circumference (HC; $n = 88{,}874$), self-reported smoking status ($n = 11{,}696$) or baseline alcohol intake ($n = 6{,}199$), or had extreme anthropometric values [height greater than 244 cm or less than 122 cm ($n = 6$); BMI less than 15 kg/m^2 ($n = 48$) or greater than 60 kg/m^2 ($n = 56$); WC less than 40 cm ($n = 0$) or greater than 160 cm ($n = 14$)]. In total, 363,094 participants were included in the current analysis.

Follow-up and assessment of head and neck cancer

To identify incident cases of head and neck cancer and assess vital status of the participants during follow-up data from population-based cancer registries and mortality registries were used, with exception of France, Germany, Greece, and Naples (Italy), where a combination of different active follow-up methods were applied. The last date of follow-up varied by EPIC center, and ranged from June 2008 to December 2013.

We applied the same definition of head and neck cancer as used by the INHANCE consortium (2), which consists of five sub-sites identified by the following International Classification of Diseases [ICD10]-10 codes: oral cavity (C00.3–C00.9, C02.0–C02.3, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C06.0–C06.2, C06.8, and C06.9), oropharynx (C01.9, C02.4, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0–C10.4, C10.8, and C10.9), oral cavity, pharynx unspecified or overlapping (C02.8, C02.9, C05.8, C05.9, C14.0, C14.2, and C14.8; 5), hypopharynx (C12.9, C13.0–C13.2, C13.8, and C13.9), and larynx (C32.0–C32.3 and C32.8–C32.9). Tumor stage (I–IV) was based either on the TNM staging ($n = 169$), the categories "localized/metastatic/metastatic regional/metastatic distant" provided by study centers ($n = 176$), or was missing/unknown ($n = 492$).

Assessment of anthropometry

Body weight (kilograms) and height (centimeters) were measured according to standardized procedures without shoes during a clinic visit (25). In the "Health-conscious" group in the UK,

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

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measured data were not available from all participants; instead, self-reported anthropometric data was adjusted using prediction equations derived from a subset of participants for whom both self-reported and measured anthropometric data were available (22). WC was measured at the narrowest torso circumference or at the midpoint between the lower ribs and iliac crest according to study center, except in Norway and Umeå (Sweden), where WC was not measured. HC (centimeters) was measured over the buttocks or at the widest point. To account for between-center methodological heterogeneity, we subtracted 1.5 kg from weight and 2.0 cm from waist and hip circumference for participants who were measured while normally dressed. We subtracted 1 kg for weight for participants who were measured in light clothing (25).

Data analysis

HRs and 95% confidence intervals (95% CI) for associations between anthropometric measures of adiposity and head and neck cancer were estimated using Cox proportional hazard models with age as the time scale (time of entry: age at recruitment, time of exit: age of diagnosis of head and neck cancer, loss to follow-up or death, whichever came first). The Cox models were stratified by center, smoking status, and age at recruitment in 1-year categories. Inspection of Schoenfeld residuals indicated that the proportional hazards assumption was not violated. BMI groups were classified as follows: <22.5 kg/m^2 (lean), 22.5 to 24.9 kg/m^2 (normal weight), 25 to 29.9 kg/m^2 (overweight), and ≥30 kg/m^2 (obese); this is a modification of the standard World Health Organization BMI cut-points (26) in order to reflect BMI 22.5 to 24.9 kg/m^2 as the lowest mortality risk group (27).

The dose–response relationship was examined by fitting Cox proportional hazards models with restricted cubic splines for BMI, WC, and WHR as continuous variables, adjusted for the same covariates as before analysis. Knots were placed at the 5th, 25th, 75th, and 95th percentiles of the anthropometric measurement followed by corresponding likelihood ratio tests comparing the goodness-of-fit of the models with and without the spline terms (28, 29).

Analyses of WC and WHR were conducted with and without inclusion of BMI (continuous) as described by Pischon and colleagues (30). WC and HC were examined independently and in mutually adjusted models to evaluate the relative contribution of the components of WHR. Wald tests based on cross-product terms were used to examine potential interactions between head and neck cancer and BMI (categorical, as described above), WC, HC, and WHR across sex, smoking status and alcohol intake [nondrinkers, light drinkers (<12 g/day), or moderate/heavy drinkers (≥12 g/day)]. We also fitted models separately by head and neck cancer subsites (oral cavity, oropharynx, hypopharynx, and larynx), in which heterogeneity across sites was assessed by joint Cox proportional hazards models (31). For all models, the potential confounders selected a priori were smoking (current, former, never), education (none/primary school, technical/professional, secondary, longer education, or missing), and baseline alcohol intake [nondrinkers, >0–6 g/day, >6–12 g/day, >12–24 g/day, >24–60 g/day (men) or >24–36 (women), >60–96 g/day (men), or >36 g/day (women), >96 g/day (men)].

Sensitivity analyses were undertaken to explore adjustment for physical activity, fruit and vegetable intake, detailed smoking history [age at smoking initiation, lifetime number of cigarettes per day, current number of cigarettes per day (current smokers), and time since quitting (former smokers)], adjustment for lifetime alcohol intake [never drinkers, past heavy drinkers (women: ≥30 g/day women, men ≥60/day; during any past decade starting at age 20), and never heavy drinkers (women: never ≥30 g/day, men never ≥60 g/day)]. In further sensitivity analyses, we excluded the first three years of follow-up and restricted the analysis to stage I (localized) and stage II (metastatic) cancers in order to reduce the likelihood of including undiagnosed cases with disease-related weight loss at baseline. The impact of changes in smoking status or weight after follow-up was explored in a sub-set of participants from the EPIC-PANACEA study (described in detail elsewhere; ref. 32), from whom self-reported data were collected again 2 to 11 years after baseline (average 5 years; n = 268,185 for the present analysis). For complete correspondence to INHANCE definition of head and neck cancer, the analyses were repeated for squamous cell carcinomas only (n = 742 cases). Finally, the calibrated anthropometric data that was derived from self-reported measures from a subset of Oxford participants (n = 40,417, including 44 head and neck cancer cases) was excluded to evaluate any impact on associations detected. All analyses were conducted with SAS version 9.3 (SAS Institute Inc.).

Data sharing

For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at http://epic.iarc.fr/access/index.php.

Results

Baseline characteristics

During a median follow-up of 15.1 years, there were 584 incident head and neck cancer cases among 126,307 men, and 253 incident head and neck cancer cases among 236,787 women. The majority (88.8%) of head and neck cancer cases were squamous cell carcinomas. Baseline characteristics are presented in Table 1. Compared to the other BMI groups, lean men and women reported a higher frequency of current smoking, higher education levels and lower mean age, WC, HC, and WHR. Scatterplots of the associations between BMI (kg/m^2) and measures of central adiposity, illustrate a relatively stronger correlation between BMI and WC (Supplementary Fig. S1A) compared to BMI and WHR (Supplementary Fig. S1B).

Preliminary analyses indicated interactions by sex between head and neck cancer risk and WC (P = 0.029) and WHR (P = 0.006), therefore subsequent analyses were stratified by sex, including BMI ($P_{\text{interaction}}$ by sex, 0.077). Spline analyses indicated a nonlinear association between BMI and head and neck cancer among men ($P_{\text{nonlinearity}}$ = 0.0011; Fig. 1); the corresponding P value for women was 0.20. There was no evidence of nonlinearity in relation to head and neck cancer risk for WC, HC, or WHR among men (P = 0.060, 0.23, and 0.29, respectively) or women (P = 0.55, 0.73, and 0.74, respectively).

BMI and head and neck cancer

A greater risk of head and neck cancer was detected among men with a BMI < 22.5 kg/m^2 (HR, 1.62; 95% CI, 1.23–2.12) compared to the reference category (BMI 22.5–24.9 kg/m^2), but no associations were detected among those with relatively higher BMI classification (Table 2). Among women, there were no associations between BMI level and head and neck cancer risk (Table 2). Following stratification by smoking status, greater risk of head and

Table 1. Baseline demographic, anthropometric and lifestyle characteristics by sex and BMI group in the EPIC study

	Men[a] BMI (kg/m^2)				Women[a] BMI (kg/m^2)			
	<22.5 (n = 13,700)	22.5–24.9 (n = 29,353)	25–29.9 (n = 62,510)	≥30 (n = 20,744)	<22.5 (n = 65,653)	22.5–24.9 (n = 59,548)	25–29.9 (n = 74,972)	≥30 (n = 36,614)
Age at recruitment (years)	50.1 (12.2)	52.5 (10.1)	53.7 (9.0)	54.1 (8.6)	47.6 (11.3)	51.0 (10.3)	53.3 (9.6)	54.3 (9.2)
Follow-up (years)	13.9 (4.5)	13.9 (4.4)	13.7 (4.4)	13.1 (4.6)	14.3 (3.9)	14.3 (3.9)	14.1 (4.0)	13.8 (4.1)
WC (cm)	81.3 (5.7)	88.0 (5.3)	96.3 (6.2)	109.1 (8.1)	69.8 (5.3)	76.2 (5.7)	84.1 (7.0)	97.8 (9.7)
HC (cm)	92.9 (4.5)	96.9 (4.2)	101.6 (4.7)	109.7 (6.7)	92.7 (4.8)	98.0 (4.6)	103.9 (5.3)	115.4 (8.6)
WHR	0.88 (0.05)	0.91 (0.05)	0.95 (0.05)	1.00 (0.06)	0.75 (0.06)	0.78 (0.06)	0.81 (0.07)	0.85 (0.07)
Smoking status (%)								
Never	36.2	33.4	29.4	26.3	53.8	53.4	58.0	65.8
Former	25.6	34.6	40.8	43.5	23.1	24.9	22.8	19.4
Current	38.2	32.1	29.8	30.2	23.1	21.7	19.2	14.8
Alcohol intake, g/day (%)								
Nondrinker	7.2	6.0	6.8	8.5	10.0	12.9	19.5	30.1
>0–6 (M)/>0–3 (W)	25.7	21.6	19.9	20.6	28.7	27.8	29.3	32.7
>6–12 (M)/>3–12 (W)	17.4	17.2	16.0	14.6	33.5	32.1	28.9	23.1
>12–24	21.4	23.2	22.3	19.5	17.0	16.7	13.6	8.6
>24–60 (M)/>24–36 (W)	22.5	26.1	27.6	26.4	6.8	6.4	5.1	3.2
>60–96 (M)/>36 (W)	4.6	5.0	6.1	7.8	4.0	4.1	3.5	2.4
>96 (M)	1.3	1.0	1.4	2.6				
Education (%)								
Missing	3.2	2.5	2.0	1.7	4.4	4.4	4.0	3.5
Primary school completed	22.2	26.5	37.0	49.8	15.7	26.4	42.0	58.2
Technical/professional school	24.9	25.0	25.1	22.3	24.5	26.3	24.0	19.2
Secondary school	14.8	13.2	10.8	8.7	22.3	19.2	14.6	9.9
Longer education (incl. University degree)	35.0	32.8	25.1	17.5	33.2	23.6	15.4	9.2

[a]Data are mean (SD) unless otherwise specified. M, men; W, women.

neck cancer was detected among current smokers with BMI < 22.5 kg/m^2 (for both men and women), and a marginally significant greater risk of head and neck cancer was detected among women never smokers with BMI > 30 kg/m^2 (HR, 1.90; 95% CI, 0.98–3.71; P = 0.058). However, testing for significant interactions between head and neck cancer risk and smoking status yielded null results (P = 0.68 and 0.35 among men and women, respectively); therefore, observed variation between groups must be interpreted with caution.

WC and head and neck cancer

WC was not associated with head and neck cancer risk among men in the model adjusted for education and alcohol intake (Table 2); however, further adjustment for BMI yielded a positive association (per 5 cm: HR, 1.16; 95% CI, 1.07–1.26). In contrast, WC among women was associated with head and neck cancer risk independent of adjustment for BMI (per 5 cm: HR, 1.08; 95% CI, 1.02–1.15). There was no evidence of an interaction between WC and smoking status in relation to head and neck cancer risk for men or women, with or without adjustment for BMI.

WHR and head and neck cancer

A marginally positive association was detected by WHR and head and neck cancer risk among men (HR per 0.1 unit, 1.14; 95% CI, 0.99–1.30; P = 0.07); a stronger association was detected after adjustment for BMI (Table 2). Among women, WHR was positively associated with head and neck cancer risk (HR per 0.1 unit, 1.64; 95% CI, 1.38–1.93); this association was only marginally altered by further adjustment for BMI. A significant interaction between WHR and head and neck cancer risk across smoking groups was detected among women (P = 0.004) but not men (P = 0.63). Each 0.1 unit higher WHR was associated with a more than 2-fold higher risk of head and neck cancer among female smokers, whereas no association was detected among never or former smokers.

WC, HC, and head and neck cancer

WC and HC were both independently associated with head and neck cancer risk among men and women, with effects in opposing directions: a higher WC (per 5 cm, adjusted for HC) was associated with greater head and neck cancer risk (men: HR, 1.11; 95% CI, 1.03–1.19; women, HR 1.29; 95% CI, 1.18–1.41), whereas a higher HC (per 8 cm, adjusted for WC) was associated with lower head and neck cancer risk (men: HR, 0.69; 95% CI, 0.59–0.82; women: HR, 0.64; 95% CI, 0.53–0.76). There was no evidence of an interaction between WC (adjusted for HC) and smoking status among men or women. In contrast, for HC (adjusted for WC), the interactions in relation to smoking status were significant for women (P = 0.0002) and suggestive among men (P = 0.07), with relatively stronger effects seen among current smokers.

Among men, the results for HC were broadly similar whether or not WC was adjusted for in the analyses. Among women, however, HC without adjustment for WC was not associated with head and neck cancer risk overall, with opposing effects observed for never smokers (HR, 1.21; 95% CI, 1.01–1.33) and current smokers (HR, 0.68; 95% CI, 0.55–0.84; $P_{\text{interaction}}$ = 0.002).

Subgroup and sensitivity analyses

There was no evidence of heterogeneity across head and neck cancer subsites (oral, oropharyngeal, hypopharynx, or larynx) in relation to BMI, WC, or WHR among men or women (Table 3). In contrast, there was evidence that the association between HC (adjusted for WC) and lung cancer risk varied by head and neck cancer site among women (P = 0.033), with all HR values

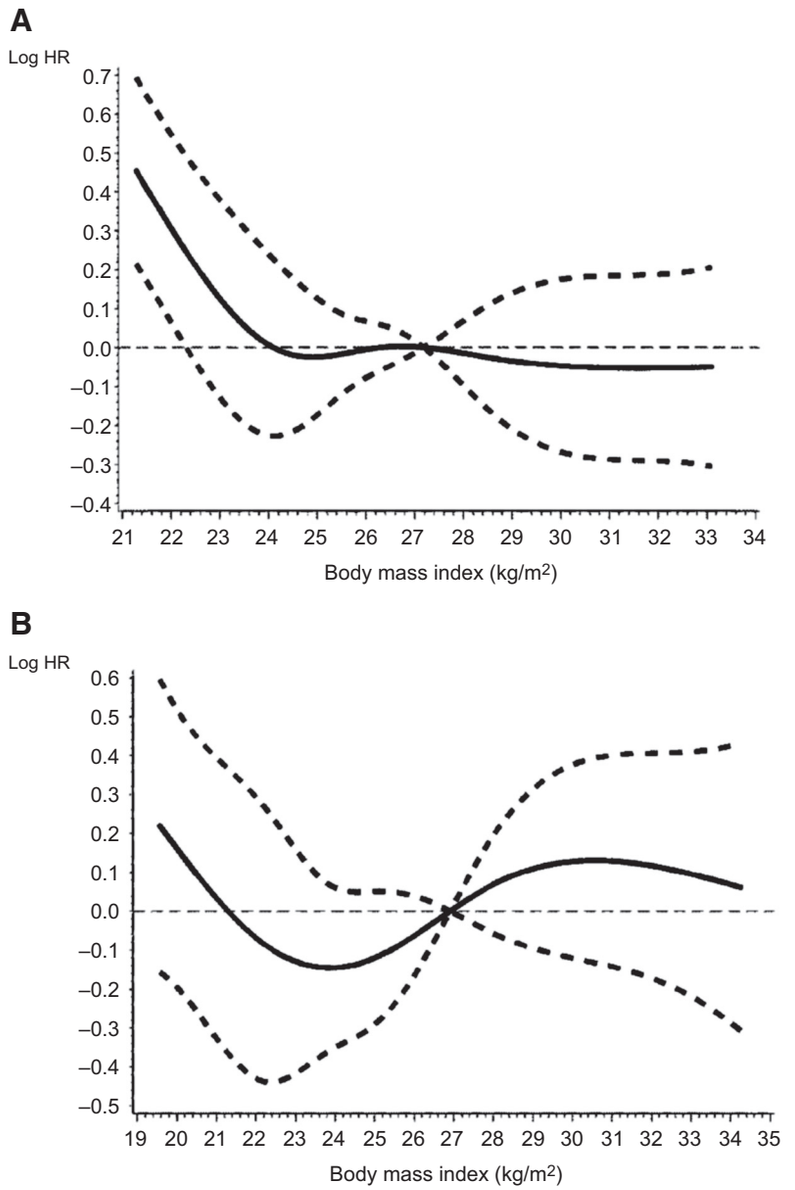

Figure 1.
Restricted cubic spline analysis of the association between measured BMI and the risk of head and neck cancer among men (**A**) and women (**B**) in EPIC; knots at the 5th, 25th, 75th, and 95th percentiles of BMI, and models adjusted for education, alcohol intake, and smoking.

significantly below 1. Similarly, tests for interactions between alcohol intake and BMI, WC, or WHR in relation to head and neck cancer risk yielded nonsignificant values (data not shown). Additional adjustment for details of smoking history [age at smoking initiation, lifetime number of cigarettes per day, current number of cigarettes per day (current smokers), and time since quitting (former smokers)], lifetime alcohol intake, fruit and vegetable intake, physical activity, exclusion of the first 3 years of follow-up, or restriction to stage I and II cancers ($n = 235$ cases) did not materially alter the results presented in Table 2 (data not shown). Similarly, additional adjustment for weight gained between baseline and the second questionnaire yielded negligible changes to the results obtained without this information included in the models (Supplementary Table S1). Upon restricting the analysis to those who were never or current smokers at baseline and at the time of the second questionnaire, results for WC, HC, and WHR in relation to head and neck cancer risk were broadly unchanged among men and women (Supplementary Table S2); as an exception, WC among never smoking men was significantly associated with head and neck cancer risk (HR, 1.26; 95% CI, 1.04–1.53). The corresponding analysis for BMI yielded null results for men and women (Supplementary Table S2); however, the reduction in the number of head and neck cancer cases per BMI subgroup is noteworthy. Following the exclusion of participants from Oxford with calibrated self-reported anthropometric measurements, there were no material changes to the results obtained for measures of adiposity and head and neck cancer among men (Supplementary Table S3). Among women, excluding the calibrated self-reported values yielded more strongly positive associations with head and neck cancer risk for those with low BMI (HR, 1.58; 95% CI, 1.06–2.36), among obese never smokers (HR 2.33; 95% CI, 1.10–4.93) and among low BMI current smokers (HR, 2.22;

Table 2. Measures of adiposity and the risk of head and neck cancer among EPIC participants, by smoking status

	All participants		Never		Former		Current		$P_{interaction}$ smoking status
	n cases	HR (95% CI)[a]	*n* cases	HR (95% CI)[b]	*n* cases	HR (95% CI)[b]	*n* cases	HR (95% CI)[b]	
Men									
BMI									
<22.5 kg/m^2	93	1.62 (1.23–2.12)	7	1.22 (0.48–3.09)	13	1.41 (0.73–2.73)	73	1.70 (1.24–2.34)	0.68
22.5–24.9 kg/m^2	130	1.0 (ref)	13	1.0 (ref)	30	1.0 (ref)	87	1.0 (ref)	
25–29.9 kg/m^2	270	0.92 (0.75–1.15)	28	1.22 (0.62–2.39)	86	1.00 (0.66–1.53)	156	0.85 (0.65–1.12)	
≥30 kg/m^2	91	0.88 (0.67–1.17)	8	1.14 (0.46–2.82)	31	1.04 (0.62–1.75)	52	0.78 (0.55–1.12)	
WC (per 5 cm)	584	0.98 (0.94–1.02)	56	0.94 (0.81–1.09)	160	1.03 (0.95–1.12)	368	0.96 (0.91–1.01)	0.29
WC (per 5 cm) + BMI		1.16 (1.07–1.26)		1.12 (0.95–1.33)		1.23 (1.10–1.37)		1.14 (1.04–1.25)	0.31
WHR (per 0.1 unit)	584	1.14 (0.99–1.30)	56	0.91 (0.57–1.45)	160	1.16 (0.89–1.51)	368	1.16 (0.98–1.38)	0.63
WHR (per 0.1 unit) + BMI		1.42 (1.21–1.65)		1.16 (0.72–1.88)		1.42 (1.09–1.84)		1.45 (1.21–1.74)	0.68
HC (per 8 cm)	584	0.84 (0.76–0.93)	56	0.85 (0.60–1.20)	160	1.01 (0.83–1.21)	368	0.77 (0.68–0.88)	0.077
WC (per 5 cm) + HC	584	1.11 (1.03–1.19)	56	1.06 (0.91–1.25)	160	1.17 (1.06–1.30)	368	1.09 (1.01–1.18)	0.29
HC (per 8 cm) + WC	584	0.69 (0.59–0.82)	56	0.83 (0.67–1.05)	160	0.83 (0.67–1.05)	368	0.64 (0.54–0.76)	0.070
Women									
BMI									
<22.5 kg/m^2	68	1.34 (0.94–1.93)	15	1.08 (0.53–2.21)	11	0.88 (0.40–1.93)	42	1.78 (1.06–2.97)	0.35
22.5–24.9 kg/m^2	55	1.0 (ref)	16	1.0 (ref)	15	1.0 (ref)	24	1.0 (ref)	
25–29.9 kg/m^2	89	1.26 (0.89–1.78)	31	1.25 (0.68–2.30)	22	1.02 (0.52–1.99)	36	1.45 (0.86–2.45)	
≥30 kg/m^2	41	1.37 (0.90–2.10)	23	1.91 (0.98–3.72)	8	0.99 (0.41–2.38)	10	1.03 (0.48–2.20)	
WC (per 5 cm)	253	1.08 (1.02–1.15)	85	1.12 (1.01–1.23)	56	1.04 (0.91–1.18)	112	1.08 (0.99–1.18)	0.66
WC (per 5 cm) + BMI		1.31 (1.18–1.46)		1.36 (1.19–1.56)		1.25 (1.06–1.47)		1.30 (1.15–1.48)	0.61
WHR (per 0.1 unit)	253	1.64 (1.38–1.93)	85	1.21 (0.87–1.69)	56	1.13 (0.73–1.73)	112	2.09 (1.70–2.56)	0.004
WHR (per 0.1 unit) + BMI		1.75 (1.47–2.08)		1.31 (0.93–1.83)		1.22 (0.79–1.90)		2.19 (1.78–2.70)	0.006
HC (per 8 cm)	253	0.94 (0.83–1.06)	85	1.21 (1.01–1.46)	56	1.03 (0.80–1.33)	112	0.68 (0.55–0.84)	0.002
WC (per 5 cm) + HC	253	1.29 (1.18–1.41)	85	1.34 (1.19–1.52)	56	1.24 (1.07–1.44)	112	1.28 (1.15–1.43)	0.63
HC (per 8 cm) + WC	253	0.64 (0.53–0.76)	85	0.70 (0.53–0.93)	56	0.70 (0.53–0.93)	112	0.48 (0.39–0.60)	0.0002

Abbreviations: BMI, body mass index; HC, hip circumference; WC, waist circumference; WHR, waist-to-hip ratio.
[a]Cox regression models stratified by age, sex, center, and smoking status, adjusted for education and alcohol intake.
[b]Cox regression models stratified by age, sex, center, adjusted for education and alcohol intake.

95% CI, 1.26–3.89; Supplementary Table S3). Similarly, restriction of the analysis to squamous cell carcinomas did not materially change the nature of the results detected (data not shown).

Discussion

In this large, prospective cohort of over 360,000 individuals, greater levels of central adiposity (WC and WHR) were associated with higher risk of head and neck cancer among women and men; among men, statistically significant associations for central adiposity were detected only after further adjustment for BMI. Low BMI (<22.5 kg/m^2) was associated with greater risk of head and neck cancer among men compared with the reference category (22.5–24.9 kg/m^2); stratification by smoking status yielded higher risk among male and female smokers with low BMI. However, caution is required in interpretation of this subgroup analysis due to not having found evidence for a statistically significant interaction between BMI and smoking status in relation to head and neck cancer risk. Among women, there was evidence of an interaction between WHR and smoking status in relation to head and neck cancer. Stratification by smoking yielded a strong positive association between WHR and head and neck cancer risk among current smokers among women; mutual adjustment for WC and HC indicated that this is explained by a relatively stronger protective effect of higher HC, rather than high risk associated with greater WC. The observed associations were not explained by variation in self-reported alcohol or tobacco exposure history. Similarly, the results were not materially changed by excluding the first three years of follow-up, thus reducing the likelihood of cases presenting with disease-related weight loss at baseline. There was no evidence of confounding by other lifestyle factors, including physical activity and fruit and vegetable intake, but the possibility of confounding by unknown or unmeasured factors remains. Therefore, the observed higher head and neck cancer incidence for males with low BMI, and female smokers with greater WHR values, requires confirmation in other studies.

Many of our results were consistent with those of the large cohort studies (33, 34) and pooled analysis of anthropometry and head and neck cancer (ref. 19; the latter of which included data from an earlier follow-up of the EPIC cohort). The strength of the associations detected for BMI and WHR in relation to head and neck cancer risk in the NIH-AARP study, the largest single cohort study to date on this topic (33) were broadly consistent with those reported in this study for men; it is likely that their head and neck cancer cases were predominantly men, given a higher incidence of head and neck cancer among men and the higher proportion of men (60%) in the NIH-AARP cohort (33). As in this study, the risk of head and neck cancer in the Netherlands Cohort Study (NLCS) was significantly higher among those with relatively low BMI values (34). However, further comparison of the results by smoking status is limited as there was no evidence of nonlinearity between BMI and head and neck cancer risk in NLCS and therefore BMI analyzed as a continuous variable among smoking subgroups. Similar to the present results, the pooled analysis reported that head and neck cancer risk was positively associated with WC and WHR and inversely associated with HC (among smokers only; ref. 19), but found no evidence of an interaction across smoking groups in the pooled analysis. Stronger associations were detected for the measured anthropometric data used in the present analysis compared to the pooled analysis. However, the heterogeneity in the association between BMI and head and neck

Table 3. Measures of adiposity and the risk of head and neck cancer among EPIC participants, by head and neck cancer site[a]

	Oral cancer		Oropharyngeal cancer		Hypopharynx		Larynx		$P_{heterogeneity}$
	n cases	HR (95% CI) [b]	*n* cases	HR (95% CI)[b]	*n* cases	HR (95% CI)[b]	*n* cases	HR (95% CI)[b]	head and neck cancer site
Men									
BMI									
<22.5 kg/m^2	20	1.96 (1.06–3.60)	23	1.70 (1.00–2.91)	6	0.68 (0.26–1.77)	37	1.68 (1.10–2.57)	0.56
22.5–24.9 kg/m^2	21	1.0 (ref)	31	1.0 (ref)	17	1.0 (ref)	55	1.0 (ref)	
25–29.9 kg/m^2	54	1.15 (0.66–1.95)	68	1.09 (0.70–1.68)	23	0.61 (0.33–1.15)	115	0.87 (0.63–1.21)	
≥30 kg/m^2	19	1.12 (0.58–2.13)	14	0.69 (0.36–1.30)	8	0.68 (0.28–1.67)	45	0.91 (0.60–1.36)	
WC (per 5 cm)	114	1.00 (0.91–1.10)	136	0.94 (0.86–1.03)	54	1.03 (0.88–1.20)	252	0.98 (0.92–1.05)	0.72
WC (per 5 cm) + BMI	114	1.21 (1.07–1.36)	136	1.13 (1.00–1.27)	54	1.24 (1.03–1.49)	252	1.18 (1.06–1.30)	0.73
WHR (per 0.1 unit)	114	1.26 (0.96–1.65)	136	1.00 (0.76–1.31)	54	1.42 (0.86–2.35)	252	1.12 (0.91–1.37)	0.56
WHR (per 0.1 unit) + BMI	114	1.60 (1.23–2.07)	136	1.28 (0.95–1.72)	54	1.79 (1.07–2.99)	252	1.39 (1.14–1.68)	0.53
HC (per 8 cm)	114	0.87 (0.68–1.11)	136	0.82 (0.65–1.02)	54	0.83 (0.57–1.20)	252	0.85 (0.74–0.98)	0.98
WC (per 5 cm) + HC	114	1.14 (1.02–1.27)	136	1.07 (0.97–1.18)	54	1.16 (0.98–1.37)	252	1.11 (1.02–1.21)	0.73
HC (per 8 cm) + WC	114	0.72 (0.55–0.94)	136	0.67 (0.52–0.87)	54	0.68 (0.46–1.01)	252	0.70 (0.59–0.84)	0.98
Women									
BMI									
<22.5 kg/m^2	23	1.05 (0.60–1.84)	20	1.56 (0.74–3.25)	3	3.09 (0.33–28.87)	14	1.27 (0.56–2.85)	0.10[c]
22.5–24.9 kg/m^2	26	1.0 (ref)	12	1.0 (ref)	1	1.0 (ref)	13	1.0 (ref)	
25–29.9 kg/m^2	27	0.75 (0.43–1.30)	30	2.09 (1.08–4.02)	5	5.73 (0.59–55.66)	18	1.15 (0.57–2.32)	
≥30 kg/m^2	23	1.42 (0.79–2.54)	11	2.03 (0.88–4.65)	0	n/a	4	0.60 (0.20–1.85)	
WC (per 5 cm)	99	1.13 (1.02–1.24)	73	1.14 (1.04–1.24)	9	1.01 (0.77–1.34)	49	1.04 (0.94–1.16)	0.56
WC (per 5 cm) + BMI	99	1.40 (1.22–1.61)		1.42 (1.25–1.61)	9	1.25 (0.92–1.72)	49	1.30 (1.11–1.51)	0.57
WHR (per 0.1 unit)	99	1.72 (1.24–2.38)	73	1.68 (1.32–2.15)	9	2.00 (0.68–5.94)	49	1.71 (1.26–2.31)	0.99
WHR (per 0.1 unit) + BMI	99	1.86 (1.33–2.59)	73	1.77 (1.40–2.23)	9	2.20 (0.73–6.61)	49	1.79 (1.35–2.37)	0.97
HC (per 8 cm)	99	1.06 (0.87–1.29)	73	1.04 (0.85–1.26)	9	0.66 (0.47–0.91)	49	0.79 (0.58–1.09)	0.042
WC (per 5 cm) + HC	99	1.35 (1.19–1.53)	73	1.35 (1.20–1.52)	9	1.21 (0.90–1.64)	49	1.24 (1.08–1.41)	0.56
HC (per 8 cm) + WC	99	0.70 (0.55–0.89)	73	0.69 (0.55–0.87)	9	0.43 (0.31–0.61)	49	0.54 (0.41–0.71)	0.033

Abbreviations: BMI, body mass index; HC, hip circumference; WC, waist circumference; WHR, waist-to-hip ratio.

[a]Head and neck cancer site was defined as oro/hypopharynx not otherwise specified among 23 women and 28 men.

[b]Cox regression models stratified by age, sex, center, and smoking status, adjusted for education and alcohol intake.

[c]Among women, the test for interaction between BMI classification and tumor site excluded hypopharynx due to the absence of any cases of hypopharyngeal cancer among BMI 25 to 29.9 kg/m^2.

cancer by smoking status in the pooled analysis was not replicated in this study; this may have been due to limited head and neck cancer cases in some BMI groups. The pooled consortium study is the largest analysis to date, and comprised predominantly self-reported anthropometric data (including some EPIC centers where only self-reported data was collected). Discrepancies in results between the present and the pooled analysis may be due to factors other than error introduced by self-reported anthropometry; for example, in the consortium analysis adjustment was made for genetic ancestry. However, the impact of misclassification by self-reported anthropometry is well-established, particularly when categories are used as the unit of analysis (22). If central adiposity is positively associated with head and neck cancer risk, evidence that self-reported WC and WHR values are lower among those with greater BMI and larger waist size (35, 36) suggests that estimates of self-reported central adiposity and head and neck cancer risk may be biased toward the null. Overall, the pooled consortium study provided strong evidence of a positive association between adiposity and head and neck cancer, particularly for abdominal obesity and among never smokers, and had a substantial sample size that enabled thorough study of subgroups. The results from the present analysis further support the findings of the pooled analysis and highlight the urgency to implement effective policies to reduce obesity.

A novel observation that emerged from the present analysis was relative strength of association between central adiposity and head and neck cancer risk among women compared to men, and the apparent inverse association between HC (adjusted for WC) and head and neck cancer risk, particularly among smokers. Previously within the EPIC cohort, WC-adjusted HC has been positively associated with the risk of esophageal cancer, although no interactions by smoking status were detected (16).

It has been proposed that greater subcutaneous fat storage on the hips may be associated with reduced cancer risk by serving as a "metabolic sink" to prevent lipotoxic effects (37, 38), but this mechanism has not been established. Similarly, as there are no established biological pathways for an association between adiposity and head and neck cancer risk, it is difficult to speculate why such effects might differ by sex. Proposed mechanisms for adiposity-cancer associations include insulin and insulin-like growth factors, sex steroids, adipokines, and systematic inflammation (39). These proposed pathways are supported by evidence from cohort studies and randomized controlled trials that intentional weight loss is associated with lower levels of estrogen, estradiol, inflammatory markers, and lower incidence of cancers at a range of sites (40). Mechanistic evidence regarding adiposity and head and neck cancer is limited, but includes a small study of laryngeal cancer patients in which higher levels of leptin expression were detected in tumor tissue compared with healthy tissue, and a positive association between leptin expression and cancer recurrence was noted (41). Excess adipose tissue is typically stored centrally for men but gluteofemorally for women (42); therefore, the accumulation of central adiposity among women may be indicative of metabolic imbalances (i.e., excess androgens, as noted in polycystic ovarian syndrome; ref. 43) that would not be observed among men. Given the novelty of the present findings, further sex-stratified analysis in other populations is

required to confirm that these differences are pervasive in the context of measured anthropometry.

BMI-adjusted central adiposity was associated with head and neck cancer in the present analysis; however, we would advise caution in the interpretation of mutually adjusted anthropometric values. WC and WHR are both highly correlated with BMI, and so the interpretation of relative risks for an increment in these variables for a given BMI is not straightforward. That is, for a given fixed BMI the variability in WC and WHR is limited. The adjustment for multiple aspects of anthropometry in relation to head and neck cancer is particularly complex within the context of smoking status. BMI is typically lower among current smokers than among former or never smokers (44–47), possibly as a result of decreased appetite (48), higher resting metabolic rate (49–51), or morbid conditions that make them lean. Smokers, despite lower weight, also have a higher WC, lower HC, and higher WHR values than nonsmokers on average (52). These differences are more pronounced among smokers with relatively greater smoking intensity and former smokers with comparatively shorter duration since quitting, and are not attenuated by adjustment for physical activity, energy intake, alcohol intake, and education (46). Possible explanations for these differences are proposed estrogenic effects of smoking (53), or uncontrolled confounding for self-reported factors that are prone to error (e.g., lower HC among current smokers could reflect lower physical activity and consequent muscle wasting in the gluteal region).

Strengths of this include the prospective design, availability of measured anthropometry, wide range of exposure values, and large sample size that enabled stratification by smoking status. The availability of detailed data on past smoking habits and alcohol intake facilitated thorough evaluation for potential confounding through these exposures. However, the study has also some limitations. First, there were a relatively small number of cases in some BMI groups in the analyses run separately by smoking status and by head and neck cancer site, particularly among never smokers and for cancers of the hypopharynx; the power for related interaction tests may have been limited, particularly among women. Further, there is uncertainty as to what the most appropriate reference category and classification system ought to be applied to BMI: the present analysis combined all individuals with BMI < 22.5 kg/m^2, using 22.5 to 24.9 kg/m^2 as the reference group. The WHO classification system identifies those with BMI < 18.5 kg/m^2 as underweight; therefore, we may have reduced our ability to detect associations between underweight and head and neck cancer by setting our lowest category as 15.0 to 22.5 kg/m^2. However, there was a limited number of participants with measured BMI < 18.5 kg/m^2 ($n = 4{,}604$, including six male and four female head and neck cancer cases); therefore, the impact of combining underweight and low-normal weight individuals in this is unlikely to have been substantial. The spline analysis indicated that the BMI values with the lowest risk of head and neck cancer may differ for men and women, as does the magnitude of risk associated with relatively lower BMI values; further research is needed to confirm and characterize these differences by sex. Finally, the use of measured anthropometry in this yielded larger effect sizes than seen in previous research where self-report has been used, and we propose that this discrepancy may be due to the error that is known to exist for self-report. However, this cannot be confirmed in the absence of both measured and self-reported data on the same subjects. We could not undertake such a comparison as the majority of EPIC participants had measured anthropometry only, with only 12% of the present sample having both measured and self-reported values.

Summary

This analysis yielded evidence of a positive association between central adiposity and head and neck cancer, particularly among women, with larger effect sizes detected than in previous studies using self-reported anthropometry. If a causal association exists between adiposity and head and neck cancer, the increases in global obesity prevalence observed over time (54) may also result in higher incidence of head and neck cancer. In addition to continued emphasis on smoking cessation, efforts to address the prevalence of obesity may therefore contribute to lower incidence of head and neck cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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