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ABSENCE OF EXCESS BODY FATNESS

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2.2.22 Cancers of the head and neck

Head and neck cancer refers to a group of cancers that develop in (i) the oral cavity; (ii) the pharynx, including the nasopharynx, the oropharynx, and the hypopharynx; (iii) the larynx; (iv) the paranasal sinuses and the nasal cavity; and (v) the salivary glands.

Most head and neck cancers are squamous cell carcinomas. Because of the established associations of head and neck cancer with tobacco use, and because BMI is inversely associated with tobacco use, it is important that associations of BMI with risk of head and neck cancers carefully consider potential confounding and/or effect modification by tobacco use. Notably, only prospective studies with at least 50 cases for any specific site were included in this review.

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and cancers of the head and neck was *inadequate*.

(a) Cohort studies

See Table 2.2.22a (web only, available at: http://publications.iarc.fr/570).

(i) Cancer of the oral cavity

The association between BMI and risk of cancer of the oral cavity has been examined in two individual prospective studies (Bhaskaran et al., 2014; Etemadi et al., 2014) and in a large pooled analysis of data from 20 prospective studies (Gaudet et al., 2015). All of these studies adjusted for both tobacco use and alcohol consumption. In the United Kingdom data linkage study of more than 5 million men and women, there was a statistically significant inverse association (RR per 5 kg/m^2 increase in BMI, 0.81; 95% CI, 0.74–0.89; $P_{trend} < 0.0001$) (Bhaskaran et al., 2014). No significant association was observed in the NIH-AARP cohort study in the USA (Etemadi et al., 2014) or in the large pooled analysis (Gaudet et al., 2015).

In contrast, quartiles of waist circumference were positively associated with risk (RR for highest vs lowest quartile, 2.00; 95% CI. 1.24–3.23; $P_{trend} < 0.001$) in the NIH-AARP study (Etemadi et al., 2014). Similarly, in the large pooled analysis of 20 prospective studies, there was a 9% increase in risk (95% CI, 1.03–1.16) per 5 cm increase in waist circumference ($P_{trend} = 0.006$) (Gaudet et al., 2015).

(ii) Cancers of the pharynx (nasopharynx, oropharynx, and/or hypopharynx)

There was no association between BMI and risk of nasopharyngeal cancer in the only study that assessed this relationship (Samanic et al., 2004). Similarly, there is no evidence that BMI is associated with risk of oropharyngeal cancer incidence (Gaudet et al., 2012, 2015) or mortality (Gaudet et al., 2012), or with hypopharyngeal cancer incidence (Gaudet et al., 2015). In the NIH-AARP cohort, BMI < 18.5 kg/m^2 was associated with a higher risk of oropharyngeal and hypopharyngeal cancer incidence compared with BMI 18.5– < 25 kg/m^2 (Etemadi et al. 2014). [There were only three cases in the exposed group.]

Waist circumference was not associated with oropharyngeal or hypopharyngeal cancer incidence in the NIH-AARP cohort study (Etemadi et al., 2014) or in the large pooled analysis (Gaudet et al., 2015).

(iii) Cancer of the larynx

Since 2000, there have been two individual prospective studies (Samanic et al., 2004; Etemadi et al., 2014) and one large pooled analysis of 20 prospective studies (Gaudet et al., 2015) of the association between BMI and risk of cancer of the larynx (Table 2.2.22a, web only, available at: http://publications.iarc.fr/570). In the large study of more than 4.5 million United States Veterans, there was a statistically significantly lower risk

of laryngeal cancer for obese compared with non-obese White and Black men (Samanic et al., 2004). [Neither tobacco use nor alcohol consumption was included in the statistical model; therefore, confounding by these factors is likely.] In the NIH-AARP cohort study in the USA, in which both tobacco use and alcohol consumption were adjusted for in the model, BMI was not associated with risk of laryngeal cancer (Etemadi et al., 2014). Conversely, in the pooled analysis, there was a statistically significant positive association between BMI and risk (RR per 5 kg/m^2 increase, 1.42; 95% CI, 1.19–1.70) (Gaudet et al., 2015).

In the NIH-AARP study (Etemadi et al., 2014), there was no evidence of an association between waist circumference and risk of laryngeal cancer, whereas a weak positive association was reported in the pooled analysis (RR per 5 cm increase, 1.10; 95% CI, 0.99–1.22; P_{trend} = 0.08) (Gaudet et al., 2015).

(iv) Cancer of the oral cavity, pharynx, and larynx combined

In two studies, the Asia-Pacific Cohort Studies Collaboration (Parr et al., 2010) and the Cancer Prevention Study II (Gaudet et al., 2012), BMI was inversely associated with death from cancer of the oral cavity, pharynx, and larynx combined. In contrast, in the pooled analysis, an incremental increase in BMI of 5 kg/m^2 was associated with a 36% increase in risk (Gaudet et al., 2015). Results from the Agricultural Health Study (Andreotti et al., 2010) were inconclusive.

The association between waist circumference and the risk of cancer of the oral cavity, pharynx, and larynx combined was examined in the large pooled analysis of 20 prospective studies, and no evidence of association was observed (Gaudet et al., 2015).

(v) Cancer of the salivary glands

There has been only one study of the association between BMI and incidence of salivary gland cancer (Samanic et al., 2004). In that study, being obese was not associated with a higher incidence compared with being non-obese in either White men or Black men.

(vi) Cancer of the head and neck or upper aerodigestive tract

For head and neck cancer incidence overall, in the United States Veterans study there was a significantly lower risk for obese compared with non-obese Black men and White men, without adjustment for tobacco use or alcohol consumption (Samanic et al., 2004). Most other prospective studies found a weak inverse association or no association between BMI at baseline and incidence of head and neck cancer (Wolk et al., 2001; Gaudet et al., 2012; Hashibe et al., 2013; Etemadi et al., 2014). When the pooled analysis of data from 20 prospective studies was stratified by smoking status, BMI was positively associated with risk in never-smokers but was inversely associated with risk in current smokers (Gaudet et al., 2015).

BMI was inversely associated with head and neck cancer mortality ($P_{trend} = 3 \times 10^{-10}$) in the Cancer Prevention Study II in the USA (Gaudet et al., 2012), and in a smaller cohort study in Switzerland a weaker inverse association was found between BMI and death from cancer of the upper aerodigestive tract (Meyer et al., 2015).

In the only study that examined the association between BMI at younger ages and risk of head and neck cancer, no association was found with increased BMI at age 20 years or at age 50 years, or with percentage change in BMI from age 20 years or age 50 years to baseline (Hashibe et al., 2013).

Waist circumference was positively associated with risk of head and neck cancer incidence both in the NIH-AARP cohort study (Etemadi et al., 2014) and in the pooled analysis of 20 prospective studies, in which a 5 cm increase in waist circumference was associated with a 4% increase in risk (95% CI, 1.03–1.05) (Gaudet et al., 2015).

(b) Case–control studies

Since 2000, a total of seven independent case–control studies, conducted in Australia, China, Cuba, India, Europe, Sudan, and the USA, and one large multicentre case–control study (nine countries) have reported on the association of BMI with various combinations of cancers of the head and neck (Table 2.2.22b, web only, available at: http://publications.iarc.fr/570). In addition, Gaudet at al. (2010) and Lubin et al. (2010, 2011) performed pooled reanalyses of 15–17 case–control studies with stratification by smoking status, by alcohol consumption status, and by subsite (Table 2.2.22c, web only, available at: http://publications.iarc.fr/570).

In most studies, BMI was assessed on the basis of self-reported height and body weight, referring to either a recent period (mostly 1 or 2 years) before disease diagnosis or to a period in the more distant past (e.g. at age 30 years). All original studies adjusted for potential confounding by smoking or alcohol consumption, in addition to variable adjustments for other potential confounding factors.

Most of the studies found an inverse association of BMI with cancer risk. In several studies, compared with normal-weight individuals (18.5 kg/m^2 ≤ BMI < 25 kg/m^2), those who were overweight or obese had reduced risks of head and neck cancer (Rajkumar et al., 2003; Rodriguez et al., 2004; Kreimer et al., 2006; Peters et al., 2008; Radoï et al., 2013; Petrick et al., 2014 in African Americans only); being underweight (BMI < 18.5 kg/m^2) was associated with an approximately 2-fold increase in risk in two large-scale studies (French ICARE study, 689 cases and 3481 controls, Radoï et al., 2013; United States CHANCE study, 1289 cases and 1361 controls, Petrick et al., 2014). In the one study that additionally reported recalled body weight at age 30 years (Radoï et al., 2013), this inverse association was also observed for past BMI.

Four case–control studies stratified the analyses by smoking status. In one early study in the USA, the inverse association was more pronounced in current or ever-smokers than in never-smokers (Kabat et al., 1994). In two more recent studies in the USA, a similar pattern was observed in African Americans but not in Whites (Petrick et al., 2014) and in both HPV-positive and HPV-negative individuals (Tan et al., 2015). In contrast, the IARC Multicenter Oral Cancer Study, which included a total of 1670 cases and 1732 controls from nine countries worldwide, found statistically significant inverse associations of BMI (country-specific tertiles) with risk of oral and oropharyngeal squamous cell carcinomas in both tobacco users and never-users, as well as in alcohol consumers and never-drinkers (Kreimer et al., 2006). Similarly, a pooled reanalysis of the data from 17 case–control studies, which included a total of 12 716 cases and 17 438 controls (INHANCE consortium; Gaudet et al., 2010) (see Table 2.2.22c, web only, available at: http://publications.iarc.fr/570), found inverse relationships of BMI with the risk of cancers of the oral cavity, pharynx, and larynx, in men and women combined, in ever-smokers (for BMI ≥ 30 kg/m^2 vs 18.5– < 25 kg/m^2: OR, 0.38; 95% CI, 0.30–0.49) but not in never-smokers. Furthermore, the increase in risk in underweight (BMI < 18.5 kg/m^2) compared with normal-weight (18.5– < 25 kg/m^2) individuals was significant only in the smokers (OR, 2.13; 95% CI, 1.75–2.58) (Gaudet et al., 2010).

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