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ABSENCE OF EXCESS BODY FATNESS

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2.2.8 Cancer of the lung

The lung is the leading cancer site for deaths, accounting for about 19% of all deaths from cancer. Most (80–90%) cases of lung cancer can be attributed to long-term smoking. Because of the large influence of tobacco smoking, any errors in estimating tobacco exposure could lead to errors in attribution of risk to any other factor known to be associated with tobacco use, including adiposity, resulting in residual confounding, even after statistical adjustment for tobacco exposure, as measured.

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 lung cancer was *inadequate*. The 2007 WCRF review concluded that there was "limited evidence suggesting that low body fatness (underweight) is a cause of lung cancer" (WCRF/AICR, 2007).

(a) Cohort studies

The evidence from cohort studies published since 2000 includes 18 reports (excluding analyses that were later updated and analyses based on fewer than 100 incident cases) and is summarized in Table 2.2.8a (web only; available at: http://publications.iarc.fr/570).

In general, studies consistently showed an inverse association between BMI and risk of lung cancer. The inverse association is linear across categories of BMI, with about 20–30% lower risk for those with BMI ≥ 30 kg/m^2. The association is generally stronger for current smokers than for never-smokers (Samanic et al., 2006; Kabat et al., 2008; Koh et al., 2010; Smith et al., 2012; Bhaskaran et al., 2014). A meta-analysis of 29 cohort studies found consistency of the association by sex and region of the world, with a relative risk estimate for obesity (compared with normal weight) of 0.78 (95% CI, 0.74–0.83) (Duan et al., 2015).

Few investigators have explored weight across the life-course as related to lung cancer risk. In general, BMI at cohort baseline (recruitment into the cohort) seems to be more strongly (inversely) associated with lung cancer risk than is BMI earlier in life (Olson et al., 2002; Fujino et al., 2007; Kabat et al., 2008; Lam et al., 2013).

Several cohorts have included measurements of waist and hip circumferences (Olson et al., 2002; Kabat et al., 2008; Bethea et al., 2013). In general, waist circumference and waist-to-hip ratio were less associated with lung cancer risk than was BMI.

(b) Case–control studies

There were a total of 11 independent reports from case–control studies on the association of BMI with lung cancer, conducted in Europe, Japan, and the USA (Table 2.2.8b, web only; available at: http://publications.iarc.fr/570). The studies were highly variable in size, some including fewer than 200 lung cancer cases, whereas others included about 1000 (El-Zein et al., 2013), more than 2000 (Brennan et al., 2009; ICARE study, France, Tarnaud et al., 2012), and more than 3000 (NECSS study, Canada, Pan et al., 2004; Kabat & Wynder, 1992). In all studies except those of Kubík et al. (2004) and Kanashiki et al. (2005), BMI was assessed on the basis of self-reported height and body weight referring to a recent period (mostly 1 year or 2 years) before disease diagnosis. Several studies collected recalled body weight in the more distant past, for example at age 20–30 years (Goodman & Wilkens, 1993; Tarleton et al., 2012; Tarnaud et al., 2012; El-Zein et al., 2013). In addition to various other adjustments for potential confounding factors, all studies except one (Heck et al., 2009) adjusted for smoking, although the degree of the adjustment varied from smoking status only (current, former, never) to lifetime cumulative exposure to tobacco smoke. The large studies by Kabat & Wynder (1992) in the USA, Pan et al. (2004) in Canada, Kanashiki et al. (2005) in Japan, and

Tarnaud et al. (2012) in France also provided estimates within separate strata of current smokers, former smokers, and never-smokers. Furthermore, one study in the USA, by Rauscher et al. (2000), provided odds ratio estimates only for former smokers and never-smokers (244 and 188 case–control pairs, respectively).

Among the studies for which the reference time frames for BMI assessment were within 5 years before lung cancer diagnosis, all studies except that of Rauscher et al. (2000), which included only former smokers and never-smokers, showed inverse associations of BMI with lung cancer risk. Several studies showed an increased risk of lung cancer particularly in individuals with low BMI, compared with individuals with BMI in the normal mid-range or higher (Tarnaud et al., 2012: OR, 2.7; 95% CI, 1.2–6.2 for BMI < 18.5 vs 18.5– < 25 kg/m^2 as reference category; El-Zein et al., 2013: OR, 2.30; 95% CI, 1.30–4.10 for BMI < 18.5 vs 18.5– < 25 kg/m^2 as reference category; and Kanashiki et al., 2005: OR, 2.0; 95% CI, 1.2–3.4 for BMI categories < 22.9 vs 22.9– < 25 kg/m^2 as reference category). However, other studies showed a more linear inverse relationship between BMI and relative risk over a wider range of BMI values, from < 18.5 kg/m^2 to > 30 kg/m^2.

In several larger studies that stratified the analysis by current smokers, former smokers, and never–smokers, an increased risk in underweight individuals, and more generally an inverse relationship between BMI and lung cancer risk, was observed only in current smokers and former smokers (Kabat & Wynder, 1992; Pan et al., 2004; Kanashiki et al., 2005; Tarleton et al., 2012; Tarnaud et al., 2012; El-Zein et al., 2013), whereas in never-smokers there was no significant association. The study of Rauscher et al. (2000), which included only former smokers and never-smokers, showed an increase in lung cancer risk with increasing BMI.

In studies that collected information about weight at ages 20–30 years, BMI in early adulthood showed no significant association (Goodman & Wilkens, 1993; Tarleton et al., 2012; El-Zein et al., 2013) with lung cancer risk or a weaker (inverse) association than that reported for BMI shortly before diagnosis (Tarnaud et al., 2012). In all four studies, cases tended to gain less weight during adult life than did controls. In one study that analysed lung cancer risk according to weight gained since early adulthood (Tarleton et al., 2012), weight gain was significantly inversely related to lung cancer risk, and more so in current smokers than in never-smokers or former smokers.

(c) Mendelian randomization studies

Two studies have applied Mendelian randomization in the context of lung cancer (Table 2.2.8c, web only; available at: http://publications.iarc.fr/570). Brennan et al. (2009) used the *FTO* rs9939609 SNP, which is robustly associated with BMI (Frayling et al., 2007; Scuteri et al., 2007; Peeters et al., 2008), as an instrument for BMI. Mendelian randomization analyses showed that each 1 kg/m^2 increase in BMI was associated with a reduced risk of lung cancer (OR, 0.85; 95% CI, 0.72–0.99; P = 0.04), including adenocarcinoma (OR, 0.51; 95% CI, 0.33–0.82; P = 0.004) and squamous cell carcinoma (OR, 0.72; 95% CI, 0.57–0.90; P = 0.01). An inverse association was observed in never-smokers (OR, 0.57; 95% CI, 0.35–0.94; P = 0.03) but not in former smokers or current smokers.

Gao et al. (2016) used genetic risk scores comprising 15 SNPs for childhood BMI and 77 SNPs for adult BMI in Mendelian randomization analyses to assess association between these measures of adiposity and all lung cancer and lung cancer subtypes. Each 1 kg/m^2 increase in adult BMI was associated with a 5% increased risk of all lung cancer (95% CI, 1.02–1.09; $P = 2.9 \times 10^{-3}$) and a 10% increased risk of squamous cell carcinoma (95% CI, 1.04–1.16; $P = 6.6 \times 10^{-4}$) (assuming that a standard deviation was equivalent to 4.5 kg/m^2). There was no association with

childhood BMI. There was minimal evidence for a positive directional pleiotropy from Mendelian randomization Egger regression, and results were null, suggesting that the positive association between adult BMI and both all lung cancer and squamous cell lung cancer may be overestimated. [The Working Group noted that interpretation of this finding is limited because individual-level data were not available on smoking status, which may be an important effect modifier. In addition, there is a potential violation of the Mendelian randomization assumptions in this analysis.]

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