

REVIEW

An update of the WCRF/AICR systematic literature review and meta-analysis on dietary and anthropometric factors and esophageal cancer risk

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Background: In the 2007 World Cancer Research Fund/American Institute for Cancer Research Second Expert Report, the expert panel judged that there was strong evidence that alcoholic drinks and body fatness increased esophageal cancer risk, whereas fruits and vegetables probably decreased its risk. The judgments were mainly based on case-control studies. As part of the Continuous Update Project, we updated the scientific evidence accumulated from cohort studies in this topic.

Methods: We updated the Continuous Update Project database up to 10 January 2017 by searching in PubMed and conducted dose-response meta-analyses to estimate summary relative risks (RRs) and 95% confidence intervals (CIs) using random effects model.

Results: A total of 57 cohort studies were included in 13 meta-analyses. Esophageal adenocarcinoma risk was inversely related to vegetable intake (RR per 100 g/day: 0.89, 95% CI: 0.80–0.99, $n = 3$) and directly associated with body mass index (RR per 5 kg/m²: 1.47, 95% CI: 1.34–1.61, $n = 9$). For esophageal squamous cell carcinoma, inverse associations were observed with fruit intake (RR for 100 g/day increment: 0.84, 95% CI: 0.75–0.94, $n = 3$) and body mass index (RR for 5 kg/m² increment: 0.64, 95% CI: 0.56–0.73, $n = 8$), and direct associations with intakes of processed meats (RR for 50 g/day increment: 1.59, 95% CI: 1.11–2.28, $n = 3$), processed and red meats (RR for 100 g/day increment: 1.37, 95% CI: 1.04–1.82, $n = 3$) and alcohol (RR for 10 g/day increment: 1.25, 95% CI: 1.12–1.41, $n = 6$).

Conclusions: Evidence from cohort studies suggested a protective role of vegetables and body weight control in esophageal adenocarcinomas development. For squamous cell carcinomas, higher intakes of red and processed meats and alcohol may increase the risk, whereas fruits intake may play a protective role.

Key words: esophageal cancer, diet, anthropometry, dose-response, meta-analysis

Introduction

Esophageal cancer is the eighth most common cancer and the eighth leading cause of cancer death in the world, with 456 000 new cases and 400 000 deaths in 2012, respectively [1]. At the time of diagnosis, only ~25% have a localized disease [2]. The 5-year survival rate is only 15%–20% in western countries [3]. Globally, there is a significant variation in esophageal cancer incidence. Esophageal squamous cell carcinoma (SCC) remains the most prevalent histologic type, particularly in ‘esophageal belt’

countries (e.g. Kazakhstan, Mongolia, Northern parts of China, Iran) [4]. In developed countries (e.g. UK [2], United States, Australia [5]), the incidence of esophageal adenocarcinoma (AC) has been increasing rapidly, exceeding the incidence of SCC.

Smoking and alcohol are the major risk factors for esophageal SCC [6]. In 2007, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AIRC) Second Expert Report [7] concluded that there was strong evidence that alcohol intake is a cause of esophageal cancer, and intake of vegetables, fruits, and foods containing β -carotene and vitamin C probably

reduce its risk; body fatness is a cause of esophageal AC, and maté probably increases the risk of esophageal SCC. For other foods and dietary components, the association with esophageal cancer was judged as 'limited'. The majority of evidence was from case-control studies and not many studies reported results specifically on esophageal SCC and AC.

Since the 2007 WCRF/AICR report, at least 70 relevant publications from prospective studies have been identified. Many of which investigated the associations by histologic types of esophageal cancer, as the etiology of the diseases is different. Modifiable risk factors are important because there are potential public health implications. We conducted an updated systematic review and meta-analysis of dietary and anthropometric factors and the risk of esophageal cancer, SCC and AC, as part of the work for the WCRF CUP [8].

Methods

Search strategy

This is an update of the 2007 WCRF/AICR report for which the search was conducted through December 2005 in eight electronic databases [7]. All cohort studies included in the report were indexed in PubMed, therefore, we updated the search in PubMed up to 10 January 2017. In addition, reference lists of relevant publications were screened for any further publications. The protocol of the CUP including the search strategy can be accessed at http://www.wcrf.org/sites/default/files/protocol_oesophageal_cancer.pdf [9].

Study selection

Included studies met the following criteria: (i) were designed as cohort, nested case-control or case-cohort study; (ii) reported relative risk (RR) estimates (hazard ratio, odds ratio, or risk ratio) with confidence intervals (CIs); (iii) reported quantifiable measures of dietary intakes or anthropometric factors. When several publications from the same study were identified, the most recent publication with the largest number of cases was selected for the review.

According to the protocol, the dose-response meta-analysis is updated in the CUP when at least two new studies had been published after the 2007 WCRF/AICR report and the total number of studies with sufficient data for meta-analysis is five or more. Additional analyses of related exposures were conducted even though the numbers did not meet the criteria.

Data extraction

The following data were extracted from each study: study characteristics (first author, publication year, country, study name, follow-up period, and losses); study sample characteristics (sex, ethnicity, number of cases and non-cases, study size); exposure details (assessment method, exposure level); outcome details (type of esophageal cancer, case ascertainment method); RR estimates and corresponding 95% CIs; and adjustment variables.

Statistical analysis

We combined the dose-response RR estimates in the studies using a random-effects model, which considers both within-study and between-study variation [10]. When the dose-response RR estimates were not available in the studies, we used Greenland and Longnecker method to derive the linear dose-response trend from the natural logarithm of the risk estimates across the exposure categories [11]. For this method, at least three categories are required, each presenting the number of person-years, cases, RRs and CIs for that category. Where this information was not provided explicitly, it was derived as specified in the protocol [9]. In brief, the following rules were applied: person-years or cases per quantile were estimated by dividing the total number of cases or person-years by the number of quantiles; missing person-years per category were estimated proportionally if the number of cases per category, RRs, and total person-years were available. When food or drinks consumption was reported in servings or times, these were converted to grams/day using standard serving sizes as stated in the protocol [9]. Where intakes were reported per 1000 kcal/day, the mean energy intake of the study population was used to estimate total intake per day. Summary RRs were estimated for men, women, and both combined. When reported separately, the RRs for men and women were first combined using a fixed effect meta-analysis before pooling with other studies. Summary RRs were calculated for any type of esophageal cancer and for SCC and AC separately. When the RRs were available by cancer types only, the combined RR for esophageal cancer was estimated using Hamling's method [12]. Hamling's method was also used to change the reference category if it did not correspond to the lowest exposure category. Floating CIs were converted to conventional 95% CIs using the method described by Orsini et al. [13]. When the study reported observed and calibrated risk estimates, the calibrated one was used for the dose-response meta-analysis.

Heterogeneity was evaluated by Cochran *Q* test and I^2 statistics [14]. The sources of heterogeneity were explored in stratified analysis by sex, cancer type (AC, SCC), geographic location, exposure assessment method, length of follow-up, number of cases, year of publication, and adjustment factors when possible. Sensitivity of the summary risk estimate was investigated in influence-analyses by excluding each study in turn.

Publication or small study bias was assessed by Egger's test and visual inspection of the funnel plot when at least five studies were included in the analysis [15]. Statistical tests with a *P* value of <0.05 were considered significant. Analyses were conducted using Stata version 12 software (Stata Corp, College Station, TX).

Results

The study search flowchart is available in Figure 1. Of the 109 publications, 57 publications from 34 different cohort studies were included in the dose-response meta-analyses of dietary and anthropometric factors and the risk of esophageal cancer, and SCC and AC. Fifteen studies were conducted in Asia, 11 in Europe, and 8 in the USA. Cases were ascertained through cancer, death or health registries, medical records, death certificates, active follow-up, or a combination of the methods. No studies were

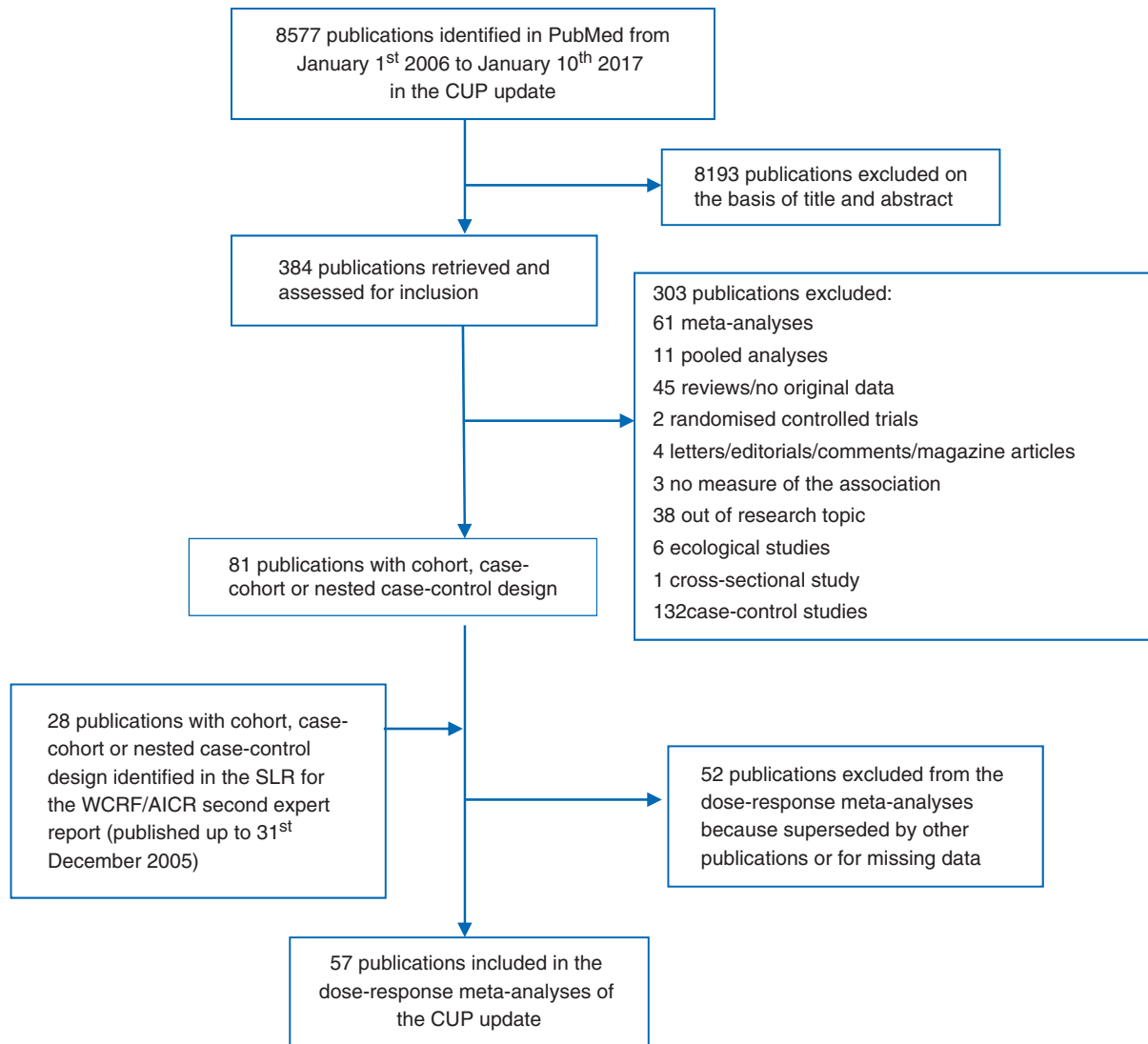


Figure 1. Flow chart of the study selection.

based on self-reported, unverified cases. Validated dietary questionnaire was used in all but one Chinese study [16–18]. Weight and height data were measured in eight studies [16, 17, 19–26], self-reported in eight [27–34] and taken from medical records in one [35]. Most studies adjusted for multiple main confounding factors such as alcohol, smoking, education, and body mass index (BMI). Main characteristics of each included publication are provided in supplementary Table S1, available at *Annals of Oncology* online. The excluded publications and reasons for exclusions are in supplementary Table S2, available at *Annals of Oncology* online.

A summary of the dose–response relationships examined in the present study is shown in Figure 2.

Fruits and vegetables

Meta-analyses were conducted for vegetables, green leafy vegetables, fruits and citrus fruits. Only two studies reported on total fruit and vegetable intake [36, 37], and found significant inverse associations with SCC [36, 37] and no association with AC [36]. There was not enough information for other vegetables or fruits [17, 38–40] (results not tabulated).

Vegetable intake was not related to the risk of esophageal cancer (all types combined) (RR per 100 g/day = 0.98, 95% CI: 0.90–1.06, $I^2 = 31%$, 5 studies) [16, 37, 38, 40, 41] and SCC (RR = 0.91, 95% CI: 0.81–1.03, $I^2 = 49%$, 4 studies) [16, 36, 37, 40], but was statistically significantly inversely associated with AC (RR = 0.89, 95% CI: 0.80–0.99, $I^2 = 0%$, 3 studies) [36, 38, 40], with one study contributing 82% weight in the analysis [36] (supplementary Figure S1, available at *Annals of Oncology* online). All three studies reported non-significant inverse associations in the analyses adjusted for multiple main confounders; of which two additionally adjusted for fruit intake [36, 40]. Green leafy vegetable intake was significantly inversely associated with the risk of esophageal cancer (RR per 50 g/day = 0.87, 95% CI: 0.77–0.98, $I^2 = 0%$, 6 studies) [17, 36–40] and AC (RR = 0.85, 95% CI: 0.74–0.96, $I^2 = 0%$, 3 studies) [36, 38, 40], but not SCC (RR = 0.89, 95% CI: 0.75–1.06, $I^2 = 0%$, 4 studies) [17, 36, 37, 40] (supplementary Figure S2, available at *Annals of Oncology* online). Only one study additionally adjusted for intake of fruits and other vegetables [40].

Fruit intake was not related to all esophageal cancer (RR per 100 g/day = 0.94, 95% CI: 0.89–1.00, $I^2 = 0%$, 4 studies) [37, 38,

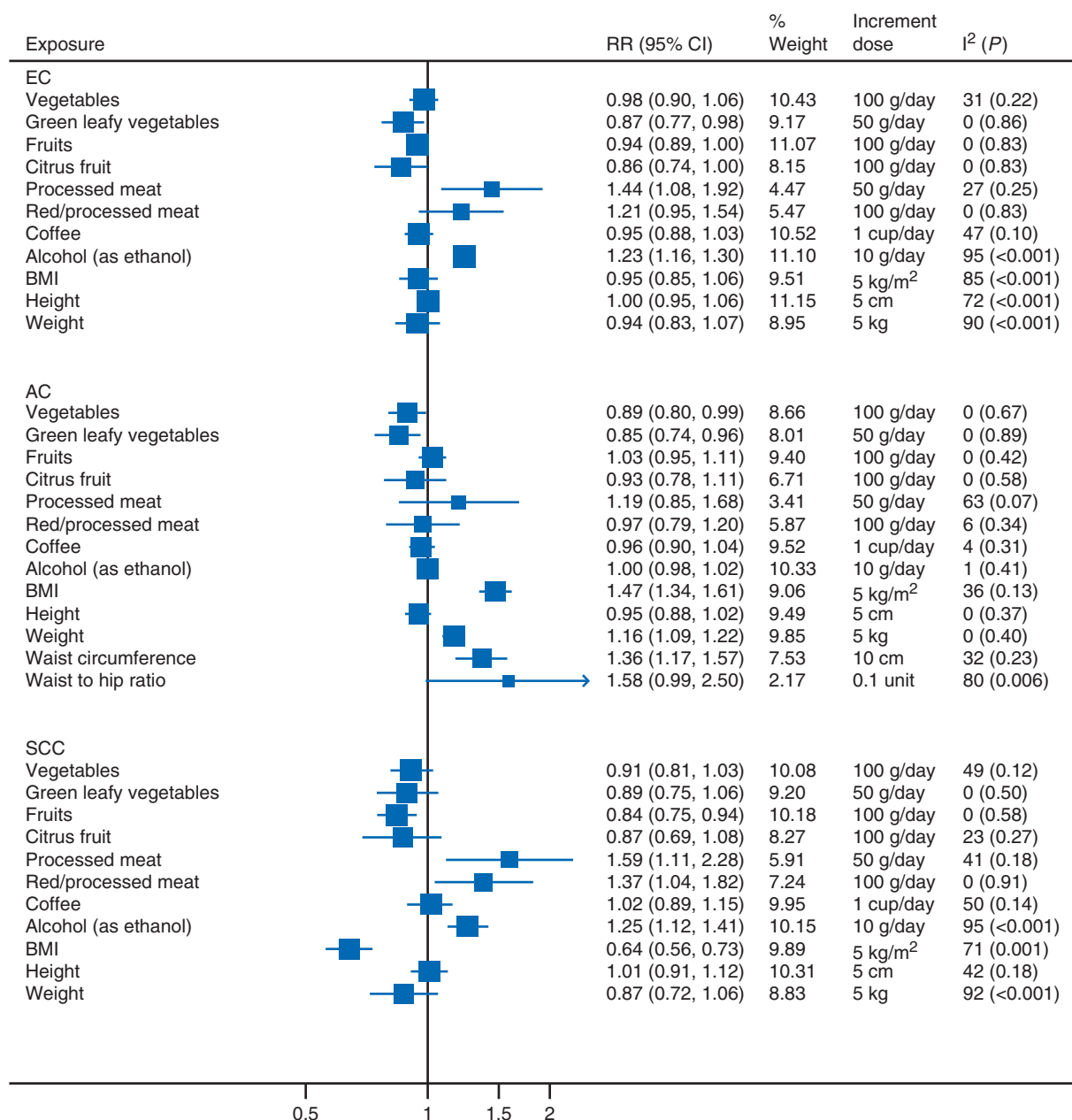


Figure 2. Summary of the dose–response relationships for the dietary and anthropometric factors and risk of esophageal cancer, adenocarcinoma and squamous cell carcinoma. EC, esophageal cancer; AC, adenocarcinoma; SCC, squamous cell carcinoma.

40, 41] and AC (RR = 1.03, 95% CI: 0.95–1.11, $I^2 = 0\%$, 3 studies) [36, 38, 40], but was inversely associated with SCC (RR = 0.84, 95% CI: 0.75–0.94, $I^2 = 0\%$, 3 studies) [36, 37, 40] (supplementary Figure S3, available at *Annals of Oncology* online). Studies on SCC adjusted for all major confounders and two studies additionally adjusted for vegetable intake [36, 40]. For citrus fruits, no significant associations were observed (supplementary Figure S4, available at *Annals of Oncology* online). The summary RRs per 100 g/day were 0.86 (95% CI: 0.74–1.00, $I^2 = 0\%$) for all esophageal cancer (6 studies) [36–40, 42], 0.93 (95% CI: 0.78–1.11, $I^2 = 0\%$) for AC (3 studies) [36, 38, 40], and 0.87 (95% CI: 0.69–1.08, $I^2 = 23\%$) for SCC (3 studies) [36, 37, 40].

In influence analyses, the results remained the same except when the only study on mortality was excluded [39], citrus fruit

became significantly inversely associated with all esophageal cancer risk (RR = 0.85, 95% CI: 0.73–0.99).

Red and processed meats

Meta-analyses were conducted for intakes of processed meat as well as processed and red meat combined. Meta-analyses were not conducted for total meat [38, 43–45], specific red meats [39, 46, 47], poultry [38, 39, 48, 49], and fish [39, 43, 45, 48, 50, 51] because of insufficient information. Reported results were mostly non-significant (results not tabulated).

Processed meat intake was associated with increased risk of all esophageal cancer (RR per 50 g/day = 1.44, 95% CI: 1.08–1.92, $I^2 = 27\%$, 4 studies) [39, 49, 52–54] (supplementary Figure S5,

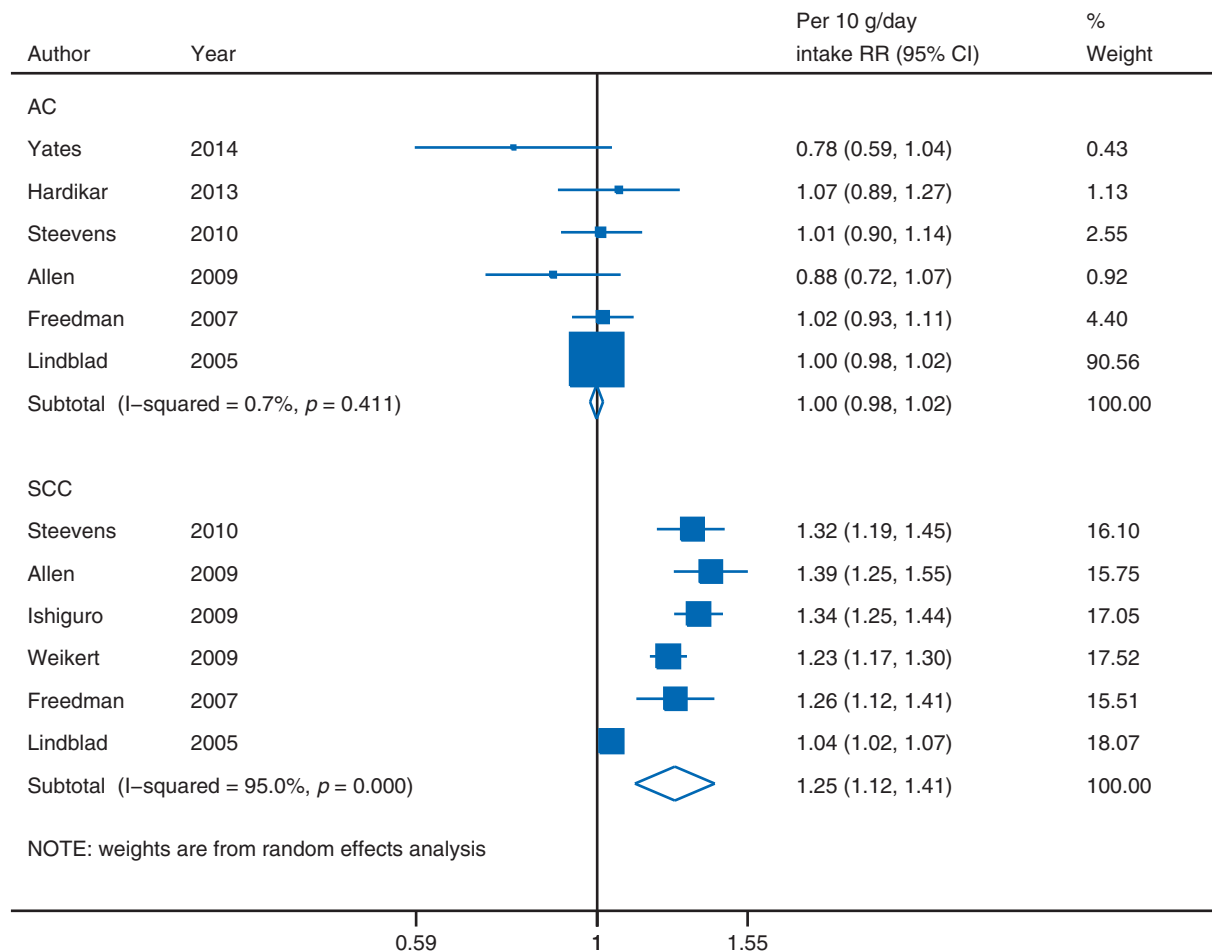


Figure 3. Alcohol intake and esophageal cancer risk by histologic type, dose–response meta-analysis. AC, adenocarcinoma; SCC, squamous cell carcinoma.

available at *Annals of Oncology* online). No significant association was observed for AC (RR = 1.19, 95% CI: 0.85–1.68, $I^2 = 63%$, 3 studies) [49, 52, 53] but a direct association was observed for SCC (RR = 1.59, 95% CI: 1.11–2.28, $I^2 = 41%$, 3 studies) [52–54].

For processed and red meat intake combined, the associations were not significant for all esophageal cancer (RR per 100 g/day = 1.21, 95% CI: 0.95–1.54, $I^2 = 0%$, 3 studies) [49, 52–54] and AC (RR = 0.97, 95% CI: 0.79–1.20, $I^2 = 6%$, 3 studies) [49, 52, 53], but was significant with SCC (RR = 1.37, 95% CI: 1.04–1.82, $I^2 = 0%$, 3 studies) [52–54] (supplementary Figure S6, available at *Annals of Oncology* online).

Hot drinks

Six [39, 55–59], two [57, 59], and three studies [57–59] were included in the meta-analyses of coffee and all esophageal cancer, AC and SCC risk, respectively. There were no significant associations (supplementary Figure S7, available at *Annals of Oncology* online). The summary RRs per 1 cup/day were 0.95 (95% CI: 0.88–1.03, $I^2 = 47%$) for all esophageal cancer, 0.96 (95% CI: 0.90–1.04, $I^2 = 4%$) for AC, and 1.02 (95% CI: 0.89–1.15, $I^2 = 50%$) for SCC.

Meta-analysis was not conducted for high-temperature drinks [16, 50, 57], tea [39, 50, 57, 59], green tea [39, 60], and black tea

[39] due to low number of studies with sufficient data (results not tabulated). Drinking hot liquid and hot tea were non-significantly inversely associated with SCC [16, 57] and AC [57] risk in two studies and significantly directly associated with esophageal cancer mortality in one study [50], comparing drinking hot versus not hot tea.

Alcoholic drinks

Alcohol intake, as measured in grams of ethanol, was significantly directly associated with all esophageal cancer risk (RR per 10 g/day = 1.23, 95% CI: 1.16–1.30, $I^2 = 95%$, 18 studies) [21, 35, 43, 50, 61–74] (supplementary Figure S8, available at *Annals of Oncology* online). The association was restricted to SCC (RR = 1.25, 95% CI: 1.12–1.41, $I^2 = 95%$, 6 studies) [35, 61, 63, 64, 69, 70] and not observed with AC (RR = 1.00, 95% CI: 0.98–1.02, $I^2 = 1%$, 6 studies) [21, 35, 61, 63, 69, 75] (Figure 3).

The substantial proportion of between-study heterogeneity in the analysis on SCC was largely due to one study [35]; when omitted in sensitivity analysis, the relationship remained similar (RR = 1.30, 95% CI: 1.24–1.36) but heterogeneity dropped from 95% to 39%. In this study, the reference category of alcohol consumption was relatively high (≤ 2 units per day), most of the study participants were in the lowest two categories, and 42% was of unknown alcohol consumption [35].

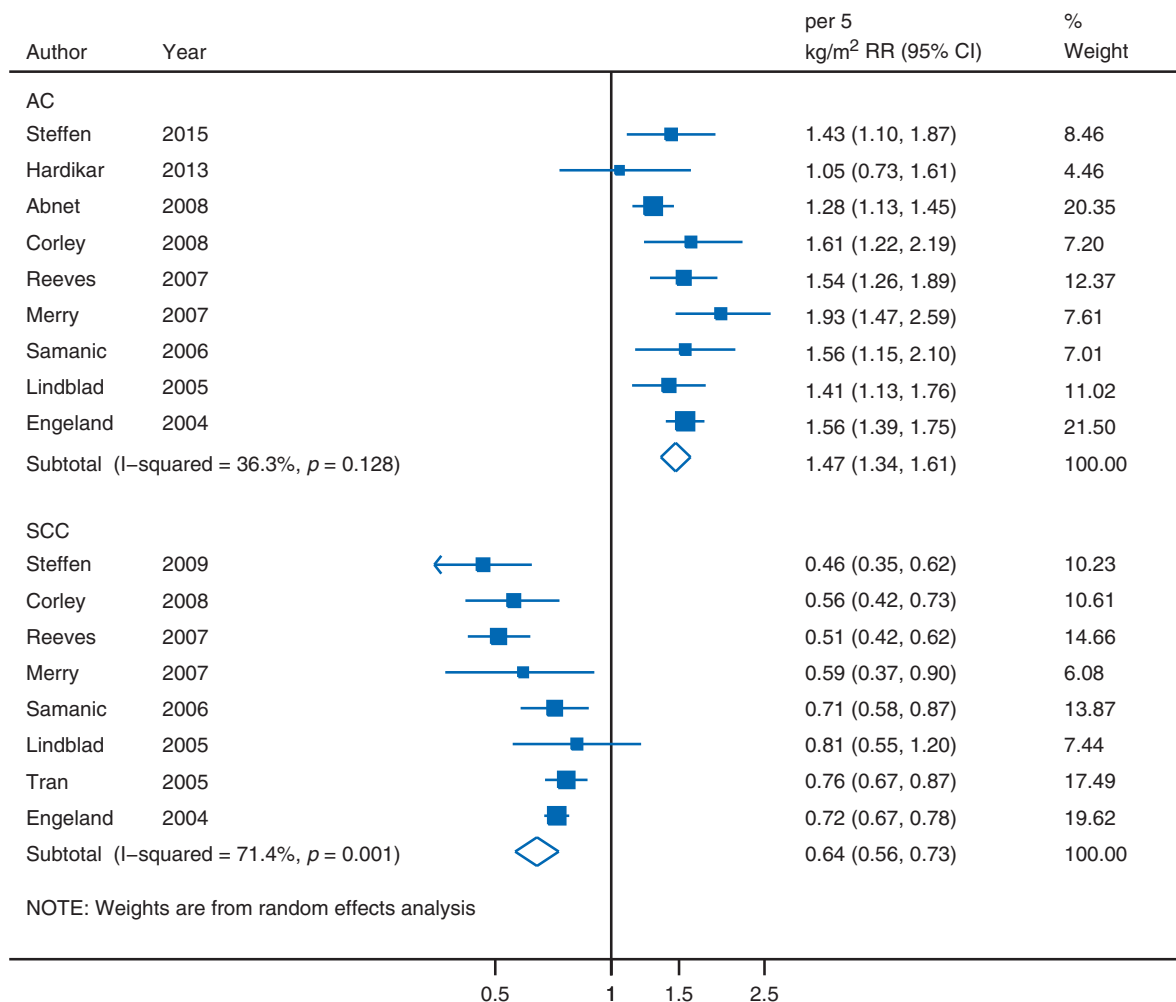


Figure 4. BMI and esophageal cancer risk by histologic type, dose–response meta-analysis. AC, adenocarcinoma; SCC, squamous cell carcinoma.

Anthropometric measurements

For BMI, 17 studies were included in the meta-analyses of esophageal cancer [16, 19–24, 26–35], nine in AC [19–21, 23, 25, 27, 33–35] and eight in SCC [16, 19, 20, 23, 26, 33–35].

BMI was not associated with all esophageal cancer risk (RR per 5 kg/m² = 0.95, 95% CI: 0.85–1.06, $I^2 = 85%$) (supplementary Figure S9, available at *Annals of Oncology* online). Significant associations, that were directly related to AC (RR = 1.47, 95% CI: 1.34–1.61) and inversely to SCC (RR = 0.64, 95% CI: 0.56–0.73) were observed (Figure 4).

The moderate ($I^2 = 36%$) and high ($I^2 = 71%$) proportions of between-study heterogeneity in the respective analyses on AC and SCC were not explained by the exposure assessment method, adjustment for smoking, geographic location, and sex; where the associations remained significant in the subgroup analyses (supplementary Table S3, available at *Annals of Oncology* online).

Meta-analyses were also conducted for weight and height; and for waist circumference and waist-to-hip ratio, where only two [25, 76] and three studies [21, 25, 76] had reported results on the risk of AC, respectively.

The associations of weight with all esophageal cancer [16, 26, 30, 76, 77], AC [25, 76] and SCC risk [16, 26] followed those

observed for BMI (supplementary Figure S10, available at *Annals of Oncology* online). Waist circumference and waist-to-hip ratio were directly associated with AC risk (supplementary Figure S11, available at *Annals of Oncology* online). The summary RRs were 1.36 (95% CI: 1.17–1.57, $I^2 = 32%$) for each 10 cm increase of waist circumference and 1.58 (95% CI: 0.99–2.50, $I^2 = 80%$) for each 0.1 unit increase of waist-to-hip ratio.

Height was not associated with esophageal cancer (RR per 5 cm = 1.00, 95% CI: 0.95–1.06, $I^2 = 72%$, 9 studies) [16, 20, 26, 30, 33, 76, 78–80], AC (RR = 0.95, 95% CI: 0.88–1.02, $I^2 = 0%$, 3 studies) [25, 33, 76] or SCC (RR = 1.01, 95% CI: 0.91–1.12, $I^2 = 42%$, 3 studies) [16, 26, 33] (supplementary Figure S12, available at *Annals of Oncology* online).

Test of publication or small study bias

Egger's test indicated significant evidence of small study bias for alcohol and esophageal cancer (all) ($P < 0.01$) and SCC ($P = 0.01$). The asymmetry in the funnel plot of SCC was driven by a study that reported a weaker association [35].

Visual inspection of the funnel plot suggested small studies reported stronger inverse associations between vegetable intake

and esophageal cancer (all) risk than expected, but the Egger's test was not statistically significant ($P=0.15$). All other P -values for Egger's test >0.18 .

Interactions with smoking: fruits and vegetables, processed and red meat, alcohol, and BMI

Studies did not observe statistically significant interactions between smoking and intakes of fruit and vegetable [36, 40], processed and red meat [52], and alcohol [44, 64, 66, 69] in relation to esophageal cancer [36, 44, 66], AC [40, 52], or SCC [37, 40, 52, 64] risks and mortality [66].

One exception was for the inverse associations of BMI with SCC risk that was only significant among smokers and not among non-smokers in the European Prospective Investigation into Cancer and Nutrition study (EPIC) (P interaction <0.01) [26]. The pooled study, Me-Can, reported similar findings but the P -values for interaction were 0.41 for current smokers and 0.59 for former smokers versus never smokers [81].

Discussion

The summary data from cohort studies indicate that esophageal AC risk is inversely associated with vegetable intake and directly associated with higher body adiposity (as assessed by BMI and waist circumference), and that the risk of esophageal SCC is inversely related to fruit intake and directly associated with intakes of red and processed meats and alcohol.

Fruits and vegetables

The estimated risk reductions were 11% for AC per 100 g/day increment of vegetable and 16% for SCC per 100 g/day increment of fruit intake. Whether vegetables and fruits have an independent role in esophageal cancer risk awaits further confirmation as not all studies included in the analyses provided mutually adjusted results. Our findings are in agreement with another meta-analysis on fruit intake [82] and SCC risk but not with a published meta-analysis that reported no association between vegetable intake and risk of AC [83]. The latter included the same prospective studies as in our meta-analysis but compared highest versus lowest intakes and did not conduct dose-response meta-analysis.

Fruits and vegetables are good sources of vitamin C and phytochemicals such as β -carotene that are tumor inhibiting, as shown in recent experimental studies [84, 85]. Risk reductions of esophageal and gastric cancers were reported in the Shandong Intervention Trial of vitamin C, E and selenium supplementation [86]; and in observational studies, inverse associations between esophageal cancer risk and dietary vitamin C intake [87], and carotenoids [88].

Red and processed meats

The summary results of cohort studies show that SCC risk increases 59% for an increment of 50 g/day of processed meats and 37% for an increment of 100 g/day of processed and red meats. A direct but not significant association of processed meat with AC was observed.

Previously published meta-analyses reported direct but not significant associations between processed meat intake and all types of esophageal cancer [89, 90] and SCC [91] risk. The present meta-analysis includes more recent publications [49, 54] with more cases. A published meta-analysis [92] reported a significant direct association with AC that was mainly influenced by case-control studies. Plausible mechanisms explaining the associations include heme iron, polycyclic aromatic hydrocarbons, dietary N-nitroso compounds (NOC) and endogenous nitrosation, that are potentially carcinogenic to humans [49, 53, 92, 93]. Direct associations between heme iron intake and risk of AC [49, 52], and SCC [93]; heterocyclic amines formed in high temperature cooked meat and AC risk [52]; dietary nitrite and risk of esophageal cancer [94] and SCC [93]; endogenous NOC index and esophageal cancer risk [94]; and intake of N-nitrosodimethylamine (NDMA) and risk of esophageal cancer [94], and SCC [93] were observed.

Hot drinks

Coffee intake was not associated with esophageal cancer risk which is in agreement with a previous meta-analysis of prospective cohort studies that compared the highest versus the lowest intakes [95]. Our meta-analysis has one additional cohort [55].

Drinking very hot beverages, traditionally at $\sim 70^\circ\text{C}$ in some areas of China, Iran, Turkey, and South America, was recently classified as probably carcinogenic to humans by the World Health Organization [96]. The epidemiologic evidence comes mainly from case-control studies, in which the direct associations were stronger than those observed in the few cohort studies that had reported results [16, 39, 50, 57, 59]. The weaker association could partly be due to the fact that these cohort studies were mostly from geographical areas where hot beverages are not normally consumed at very high temperatures. Further confirmation from prospective studies is needed.

Alcohol

Our meta-analysis showed that alcohol intake increased the risk of SCC. The results are in concordance with published meta-analyses [97, 98]. The main mechanisms implicated in the carcinogenesis are related to alcohol metabolite acetaldehyde [97] and chronic alcohol consumption induced enzymes generating reactive oxygen species [99]. The specific mechanism of SCC carcinogenesis is related to alcohol metabolism in saliva where acetaldehyde concentration is 10–100 times higher than in the blood [99]. In smokers, the conversion of acetaldehyde to non-toxic acetate in saliva is inhibited.

Anthropometry

An increment of 5 kg/m^2 of BMI was associated with 47% increased risk of AC. Weight and waist circumference were also associated with increased risk of esophageal AC. In contrast, BMI increment of 5 kg/m^2 was associated with 36% reduced risk of SCC. Our results are consistent with previously published meta-analyses on AC [100, 101] and SCC [101]. The between-study heterogeneity observed in BMI and SCC remained unexplained, but the heterogeneity was due to the magnitude rather than the direction of the associations in the studies.

The observed inverse association of BMI with SCC risk is similar to what is observed in other smoking-related cancers, as smokers have higher risk of SCC and tend to be slimmer. However, this is not supported by all studies [26]. Increased levels of estrogens associated with higher BMI may have a protective role in SCC development [26].

On the contrary, the EPIC study reported direct associations between waist circumference, and waist-to-hip ratio and the risks of SCC in smokers and non-smokers [26]. The analyses were adjusted for BMI. In agreement with this study, Lin, 2015 reported direct but not significant association for waist circumference in a multivariate-adjusted model including BMI and smoking [79]. Whether waist circumference and waist-to-hip ratio are less confounded by smoking than BMI in the association with SCC risk, independent or not of BMI, needs to be investigated further as current evidence is lacking.

Major proposed mechanisms to explain the association between body fatness and risk of cancer involve insulin, insulin-like growth factor, adipokines, inflammation, and immune responses [102]. Pressure from excess body fat in abdominal area may cause gastroesophageal reflux disease (GERD) which in turn may lead to premalignant condition of Barrett's esophagus, a precursor of esophageal AC [24].

Strengths and limitations

This meta-analysis has several strengths. In the previous WCRF/IARC systematic literature review, the evidence was mainly from case-control studies [7]. In this review, we included studies of a prospective design, preventing recall bias and providing stronger level of evidence.

We reviewed all dietary and anthropometric exposures on esophageal cancer for which dose-response meta-analyses were conducted during the Continuous Update Project (CUP), presenting an overview of available evidence on thirteen exposures. When the number of studies was sufficient, sensitivity, and stratified analyses were conducted to test the robustness of findings and explore possible sources of heterogeneity. Evidence of heterogeneity was not detected or was low for many analyses. This review particularly focuses on esophageal AC and SCC, which are more frequent in Western and Asian countries, respectively. Publications from studies based in these areas allow the examination of the differences in cancer etiology by histologic type. In terms of study quality, most studies in our review assessed dietary intake using validated food frequency questionnaires and the esophageal cancer diagnosis was documented.

The main limitation of this meta-analysis is the small number of studies on some exposures. For fruits, vegetables and red and processed meats, the small numbers in the stratified analyses reduced the possibility to detect a source of heterogeneity. Those results should be interpreted cautiously as replication is needed. For waist-to-hip ratio in relation to AC risk, sources of the significant between-study heterogeneity could not be explored as only three studies reported results; however, the direct association supported that of BMI and AC. For hot drinks, a meta-analysis was not possible as current data from prospective studies were limited.

The small number of studies reporting associations by smoking status limited a possibility to investigate confounding by

smoking. Most studies included in this review were controlled for smoking, but residual confounding cannot be ruled out. For instance, no interaction with smoking was observed in North American [36] and European [40] studies on fruits and vegetables and esophageal cancers, but in a Japanese study [37], intake of fruits and vegetables was inversely related to SCC only in current smokers and consumers of >150 g/week of alcohol. It is also possible that the association is mainly observed in smokers because smokers have lower levels of serum vitamin C [103] and may benefit more from higher intakes.

Another limitation of this meta-analysis is the lack of information in individual studies on GERD symptoms which increase the risk of Barrett's esophagus that may subsequently lead to AC. However, only ~6%–12% of those with prolonged GERD symptoms will develop premalignant lesion of Barrett's esophagus and only 0.5%–1% of these patients will be diagnosed with AC [6]. Therefore, adjusting for GERD symptoms is unlikely to significantly influence results, if not over adjusting the associations of interest for these intermediate factors.

Primary prevention of esophageal cancers may be a preferred option due to the aggressive nature of this disease and the lack of cost-effective screening. Body fatness, high alcohol and red and processed meat intakes are risk factors for other diseases and dietary patterns rich in plant foods may reduce the risk of other diseases including type 2 diabetes and CVD [104]. Therefore, existing primary prevention strategies for chronic diseases could also be used to reduce the burden of esophageal cancers.

Acknowledgements

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Disclosure

The authors have declared no conflicts of interest.

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