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REVIEW

Modifiable factors and esophageal cancer: a systematic review of published meta-analyses

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Abstract There are marked differences in the etiology of the major histological types of esophageal cancer (EC)—squamous cell carcinomas (ESCC) and adenocarcinomas (EAC). This study aimed to summarize the current scientific knowledge on modifiable risk factors for EC, by histological type, through a systematic review of meta-analyses referenced in PubMed and ISI Web of Knowledge. We identified 100 meta-analyses on risk factors for ESCC ($n = 54$), EAC ($n = 43$), or EC ($n = 51$). ESCC risk significantly increased with alcohol and maté drinking, smoking, red and processed meat consumption and human papillomavirus infection, while it was negatively associated with body mass index and consumption of fruit, vegetables, white meat, folate, and some carotenoids. Cessation of drinking and smoking significantly reduced ESCC risk. For EAC, an increased risk was reported for smoking, body mass index, and red and processed meat consumption, while risk decreased with *Helicobacter pylori* infection, low/moderate alcohol drinking, physical activity, and consumption of fruit, vegetables, folate, fiber, beta-carotene, and vitamin C. Differences in results between meta-analyses and mechanisms underlying some of the associations found are discussed. This work reinforces the importance of a separate assessment of EC subtypes to allow for a proper evaluation of incidence trends and planning of prevention/control interventions.

Keywords Review · Adenocarcinoma · Carcinoma · Squamous cell · Esophageal neoplasms · Risk factors

Introduction

There are marked differences between the tumors of the major histological types of esophageal cancer (EC) regarding incidence and mortality trends, which reflect the specificities of each subtype regarding its determinants [1].

Esophageal squamous cell carcinoma (ESCC) comprises most cases of esophageal cancer [2], although its incidence has been steadily decreasing or stabilizing in Western countries [3]. The main risk factors of ESCC occurrence are tobacco smoking and alcohol consumption and many studies have shown both the independent and synergistic effects of these determinants [4].

Esophageal adenocarcinoma (EAC) incidence rates have been steadily increasing in several Western countries [3], although there are differences, either between countries [1] and between regions within the same country [5]. The upward trends are in part due to the increased prevalence of recognized risk factors such as gastroesophageal reflux disease (GERD) and obesity [6], but they may also be explained by variation in other modifiable exposures, such as smoking, diet, and *Helicobacter pylori* (HP) infection [6–9].

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A large body of research has been devoted to studying the determinants of esophageal cancer, as summarized in several meta-analyses. This study aims to summarize the state of the art on the etiology of EC by systematically reviewing published meta-analyses on the main modifiable factors associated with the occurrence of esophageal cancer by histological type.

Methods

PubMed and ISI Web of Knowledge were searched up to September 2015 to identify published meta-analyses addressing the association between the main modifiable exposures and esophageal cancer. The titles and abstracts of the retrieved articles were read and full texts were obtained for the studies considered potentially relevant. In addition, references cited in the identified articles were manually searched.

Studies were included if a meta-analysis based on published results or an individual participant data meta-analysis was performed to quantify the association between modifiable exposures and EC, ESCC, or EAC. Only full-length papers published in English, Portuguese, Spanish, French, Italian, or Polish were included. Studies focusing on the impact of the cessation of modifiable exposures on the risk of EC, EAC, or ESCC were also kept in our review. Studies were excluded if: (1) EC, ESCC, or EAC was not reported as an outcome of interest; (2) determinants other than alcohol drinking, smoking and smokeless tobacco, HP infection, Human papillomavirus (HPV) infection, obesity/BMI, physical activity or diet were evaluated; (3) no summary estimate was provided in the form of an odds ratio (OR), relative risk (RR), or hazard ratio (HR), along with the correspondent 95% confidence interval (CI); (4) results provided constituted duplicate information from previous studies (i.e., reviews mentioning as summary estimate a result from a meta-analysis already included in our review).

Since EC is a relatively rare and a highly lethal disease, we ignored the distinction between RR, OR, and HR, reporting RR henceforth as the effect estimate. For each study, the following information was extracted: first author's name, publication year, number of studies included in the meta-analysis and corresponding study design when available, EC histological type evaluated, risk factor assessed, categories of exposure compared, the RR and corresponding 95% CI. Stratified results by sex, study type and geographical area and dose–response RRs were collected, whenever available. If both fixed and random effects estimates were provided, the latter were used as they allow for some heterogeneity between studies.

All studies were assessed independently by two researchers (CC and BP) to determine their eligibility and for data extraction; disagreements were discussed and resolved by consensus or involving a third researcher (NL).

Each meta-analysis obtained from a systematic review was attributed a quality score, ranging from 0 to 11, based on the AMSTAR tool [10]. Results obtained were summarized using a harvest plot, for the most commonly evaluated determinants. Forest plots describing the overall and sex-specific RRs on the main determinants of EAC and ESCC were obtained using Stata Statistical Software, version 11.0 [11].

Results

We identified 100 publications reporting results from meta-analyses addressing the association between the aforementioned risk factors and ESCC ($n = 54$), EAC ($n = 43$) or EC ($n = 51$). The systematic review flow-chart is presented as Supplementary Fig. S1. Information extracted for each study is accessible in Supplementary Table S1, and quality assessment is presented in Fig. 1 and Supplementary Table S2. The quality scores ranged between 3 and 10, and 50 meta-analyses had a score of 7 or higher. The main findings are presented below, and a summary of RR for the most commonly described risk factors are presented in Table 1.

Alcohol drinking

Twenty-five studies evaluated the association between alcohol drinking and EC, 11 of which did not include histology-specific RRs [12–22].

The association between ESCC and alcohol consumption was addressed in 11 studies (Fig. 2a) [23–33]. When comparing ever with never drinkers, the RR for ESCC was 3.7 among men and 2.1 among women [25]. Dose–response effects were reported in several meta-analyses [23–25, 28–30, 32, 33]. No significant differences were found between case–control and cohort studies [23, 24], nor between different geographical areas (Asia/Non-Asia [29], Europe/Asia [31] and Europe/Asia/North America [23, 24]).

Six meta-analyses reported on the relation between alcohol drinking and EAC (Fig. 2b) [27, 28, 30, 33–35]. In general, point estimates increased with alcohol consumption, but no significant associations were found in most meta-analyses, even at high levels of consumption [27, 30, 33, 35].

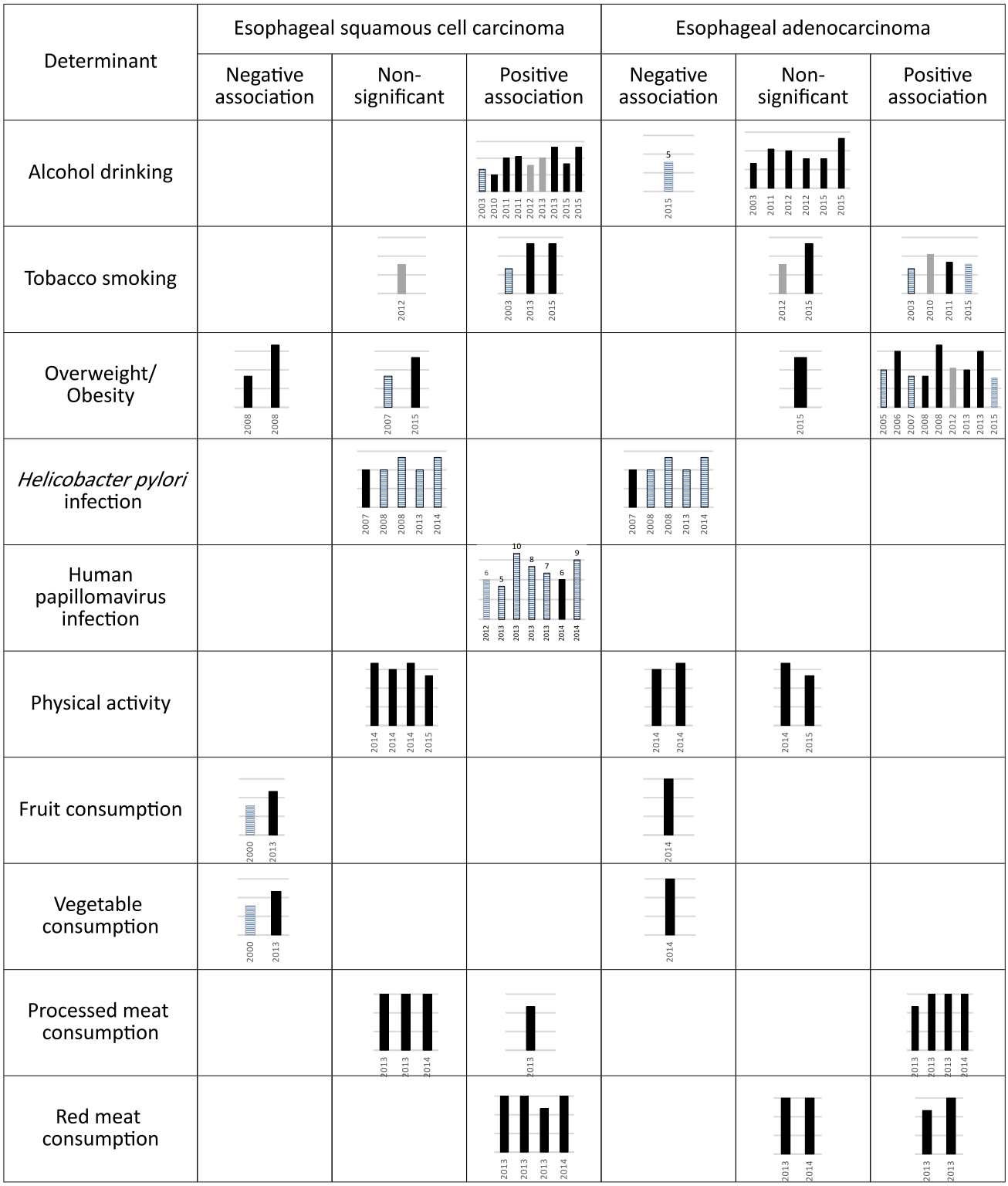

Fig. 1 Harvest plot of the overall association between the main determinants of esophageal cancer and its occurrence, by subtype, when comparing the highest with the lowest levels of exposure, infected with non-infected patients or dose–response effects. Each *bar* corresponds to a meta-analysis (based on systematic reviews in *black*, otherwise in *grey*) and depicts its quality score; labels correspond to the number of studies included in the estimate provided in each meta-analysis; an horizontal pattern indicates that the estimate was obtained from case–control studies only. Meta-analyses are ordered according to year of publication (*x*-axis)

Table 1 Relative risk (RR) estimates and corresponding 95% confidence intervals (95% CI) for the association between risk factors and incidence of esophageal cancer by histological type

Outcome	Risk factor	Categories of exposure	Subgroup	RR	95% CI	References
ESCC	Alcohol	Ever drinkers and never smokers vs. never drinkers and never smokers	Men (Western)	4.03	1.76–9.21	[25]
			Women (Western)	1.42	0.82–2.48	[25]
			Asian	1.21	0.81–1.81	[4]
	Tobacco	Ever smokers and never drinkers vs. never smokers and never drinkers	Men (Western)	4.45	2.09–9.47	[25]
			Women (Western)	1.57	0.89–2.75	[25]
			Asian	1.36	1.14–1.61	[4]
	Alcohol × smoking	Ever drinkers and ever smokers vs. never drinkers and never smokers	Men (Western)	17.00	8.36–34.78	[25]
			Women (Western)	7.26	3.68–14.33	[25]
			Asian	3.28	2.11–5.08	[4]
	Human papillomavirus infection	Infected vs. non-infected	Overall	2.69	2.05–3.54	[55]
	Body mass index	Per 5 kg/m^2 increase	Men	0.71	0.60–0.85	[64]
			Women	0.57	0.47–0.69	[64]
	Fruit consumption	Per 100 g/day increase	Overall	0.61	0.52–0.72	[104]
	Vegetable consumption	Per 100 g/day increase	Overall	0.84	0.78–0.92	[104]
	Red meat consumption	Per 100 g/day increase	Overall	1.41	1.16–1.70	[102]
EAC	Tobacco	Ever vs. never smokers	Men	2.10	1.71–2.59	[38]
		Ever vs. never smokers	Women	1.74	1.21–2.51	[38]
	Helicobacter pylori infection	Infected vs. non-infected	Overall	0.57	0.44–0.73	[54]
	Body mass index	Per 5 kg/m^2 increase	Men	1.52	1.33–1.74	[64]
			Women	1.51	1.31–1.74	[64]
	Fruit consumption	Per 100 g/day increase	Overall	0.87	0.76–0.99	[110]
	Vegetable consumption	Per 100 g/day increase	Overall	0.91	0.83–0.99	[110]
	Red meat consumption	Per 100 g/day increase	Overall	1.45	1.09–1.93	[109]

ESCC esophageal squamous cell carcinoma, *EAC* esophageal adenocarcinoma

Tobacco smoking

Fourteen studies evaluated the association between tobacco smoking and EC, EAC, or ESCC [17, 25–27, 30, 31, 33, 34, 36–41]. Using never smokers as the reference category, results obtained from the five studies not providing histology-specific RRs yielded no significant differences between sexes, study designs (case–control and cohort studies), ethnicity (African Americans, Asians, and Caucasians, though Asians had a lower point estimate) and geographical areas [17, 36, 37, 39, 40].

Six meta-analyses focused on tobacco smoking and ESCC (Fig. 3a) [25–27, 30, 31, 33]. Current smokers had a significantly higher risk of ESCC than never smokers (RR = 5.1 among men, RR = 3.1 among women) [25] and presented twice the risk of former smokers (RR = 3.13, 95% CI 2.53, 3.86 vs. RR = 1.68, 95% CI 1.44, 1.96) [31]. Dose–response effects were reported with the number of cigarettes smoked per day or per week [25, 33], the number of smoking years [25] and the number of pack-years [27, 30], using non-smokers as reference. Prabhu et al. [31] found a lower ESCC risk in Asia (RR = 2.31, 95% CI 1.78, 2.99) than in Europe (RR = 4.21, 95% CI 3.13, 5.66) when comparing current with never smokers.

Six studies reported on the association between tobacco smoking and EAC (Fig. 3b) [27, 30, 33, 34, 38, 41]. The only meta-analysis providing sex-specific estimates showed a non-significantly higher EAC risk among men (RR = 2.10 for men, RR = 1.74 for women) [38], with the strength of association being much lower than that of ESCC. As for ESCC, there was a dose–response relation [30, 33, 34, 38]. When comparing ever with never smokers, the association between smoking and EAC was found significant in two meta-analyses (RR $\approx$ 1.9) [38, 41], but not in a third one (RR = 0.96, 95% CI 0.82, 1.12, n = 4) [27].

Alcohol drinking/tobacco smoking cessation

Time since cessation of alcohol drinking (Supplementary Fig. S2A) or tobacco smoking (Supplementary Fig. S2B) was assessed in four meta-analyses [25, 26, 42, 43].

Ten or more years since cessation did not suffice to reduce ESCC risk to the values observed among never

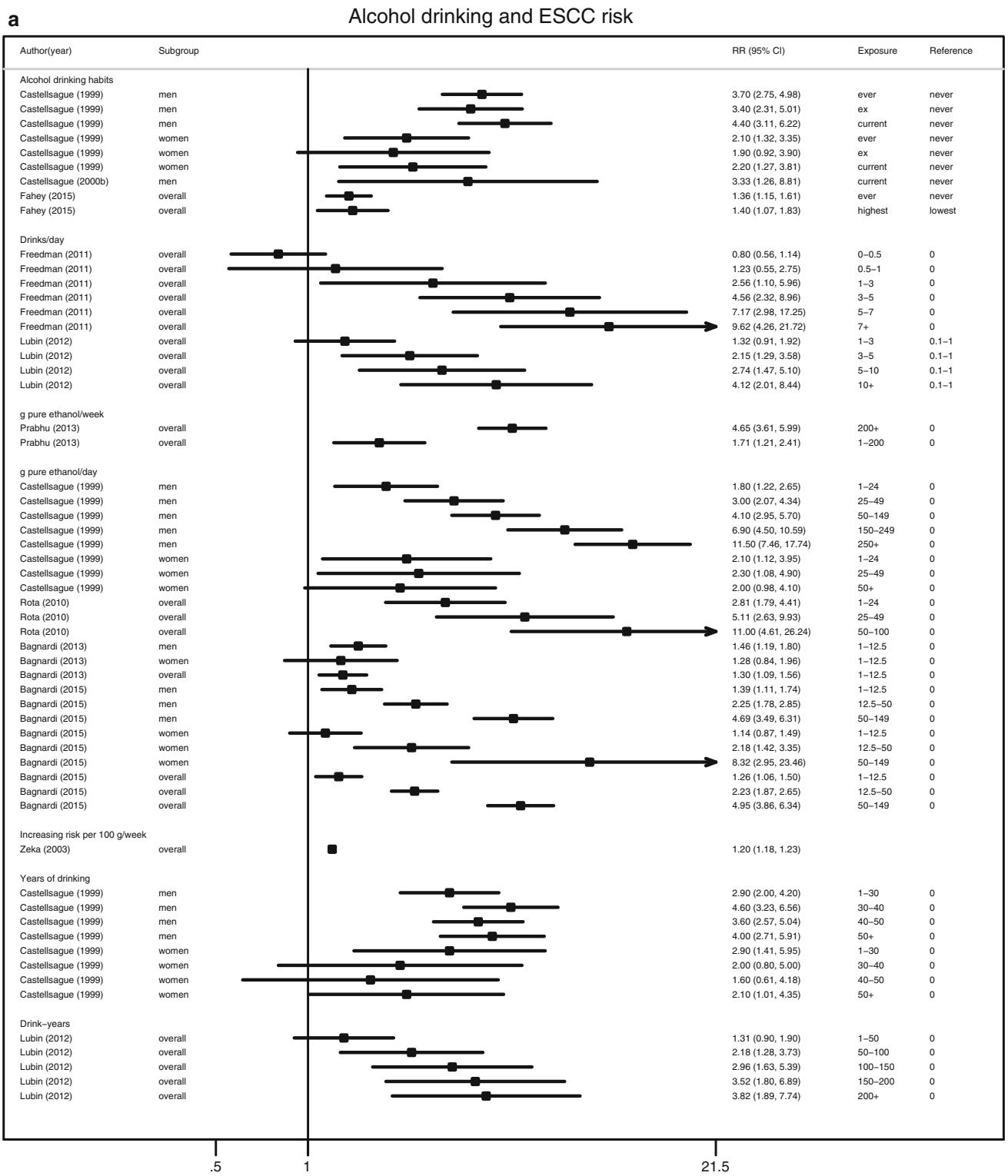

Fig. 2 Forest plots of overall and sex-specific associations between alcohol drinking and the occurrence of **a** esophageal squamous cell carcinoma (ESCC) and **b** esophageal adenocarcinoma (EAC). *RR* relative risk, *CI* confidence interval

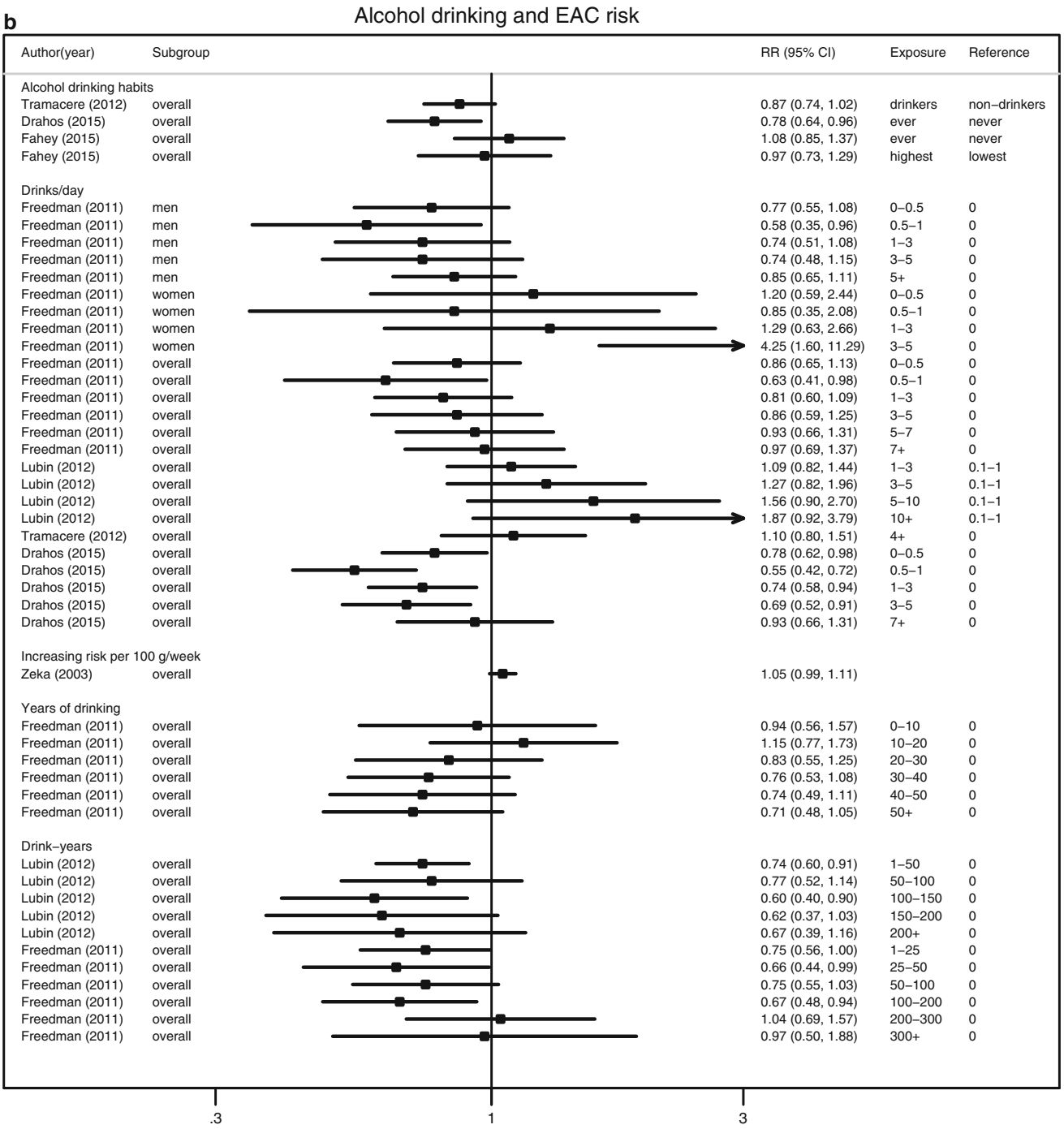

Fig. 2 continued

drinking men nor among never smoking men; among women, 5 and 10 years since cessation were enough to reach similar values to the ones obtained for never drinkers and never smokers, respectively [25]. The risk of ESCC among men was shown to decrease by 4% per year since cessation of alcohol drinking (RR = 0.96, 95% CI 0.94, 0.98) and by 2% per year since cessation of tobacco smoking (RR = 0.98, 95% CI 0.97, 0.99) [26]. No meta-analyses were found on the association between alcohol drinking cessation or tobacco smoking cessation and EAC.

Smokeless tobacco

Three meta-analyses evaluated the effects of overall smokeless tobacco on EC and yielded a significantly higher risk among ever users, although conflicting results were

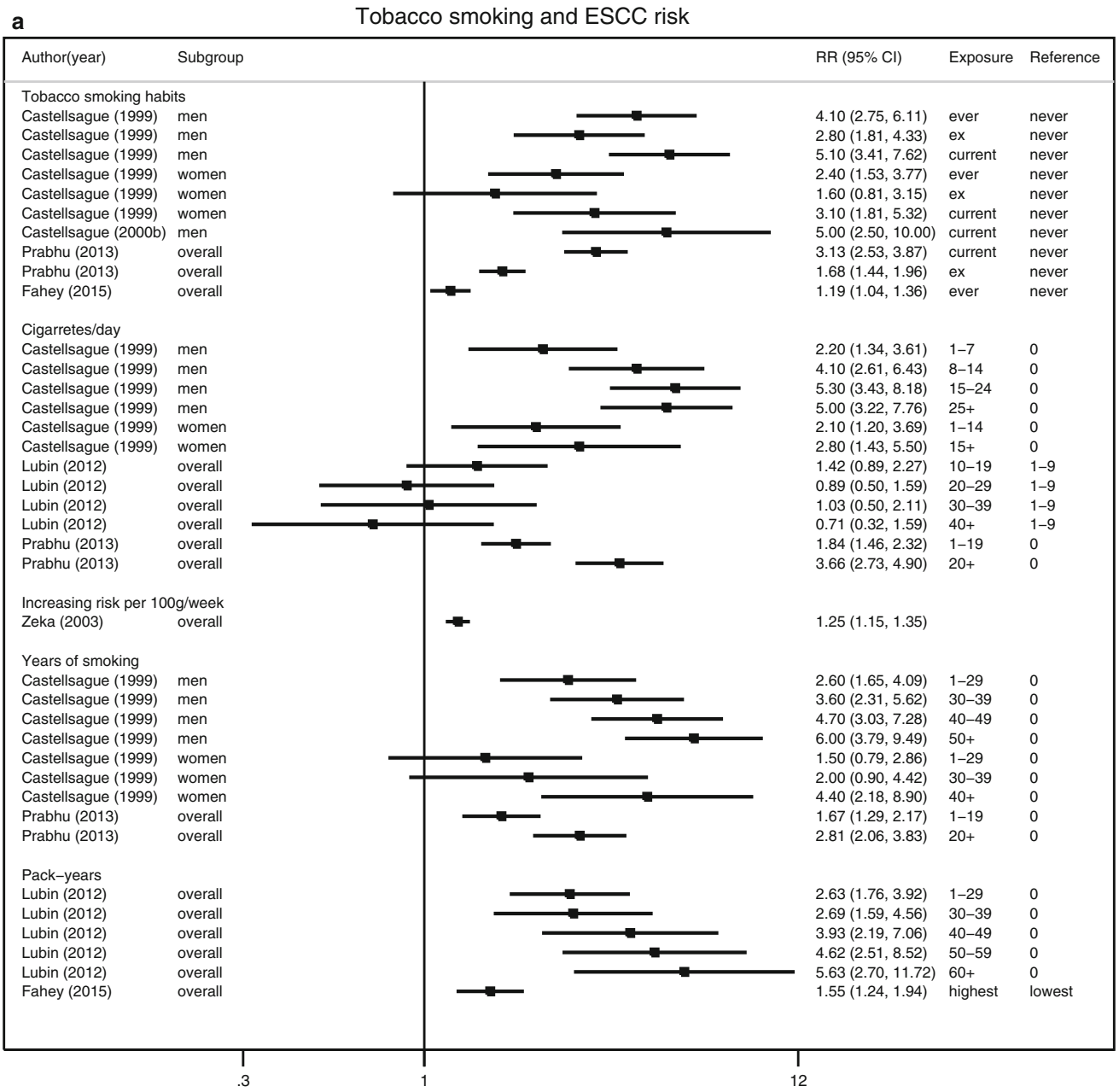

Fig. 3 Forest plots of overall and sex-specific associations between tobacco smoking and the occurrence of **a** esophageal squamous cell carcinoma (ESCC) and **b** esophageal adenocarcinoma (EAC). *RR* relative risk, *CI* confidence interval

reported when stratifying analyses by geographical area [44–46]. Akl et al. [47] reported a non-significantly higher risk of EC among current waterpipe smokers, in comparison with never smokers (RR = 1.85, 95% CI 0.95, 3.58). Akhtar et al. [48] focused on areca nut (also commonly referred to as betel nut) chewing, and reported an increased risk of ESCC for chewers in comparison with non-chewers (RR = 3.05, 95% CI 2.41, 3.87). Among never tobacco smokers, the use of snus significantly increased the risk of ESCC (RR = 3.5, 95% CI 1.6, 7.6) but not EAC (RR = 0.2, 95% CI 0.0, 1.9) [49].

HP infection

The effect of HP infection was evaluated by five meta-analyses that reported results for both ESCC and EAC (Fig. 4) [50–54]. All showed no association between HP and ESCC, while for EAC a protective effect of HP infection was found (RR ≈ 0.5). In 2013, protective effects of HP infection (RR = 0.66, 95% CI 0.43, 0.89) and infection with CagA-positive strains (RR = 0.77, 95% CI 0.65, 0.92) were reported for ESCC, when analyses were restricted to studies from Iran and China [52].

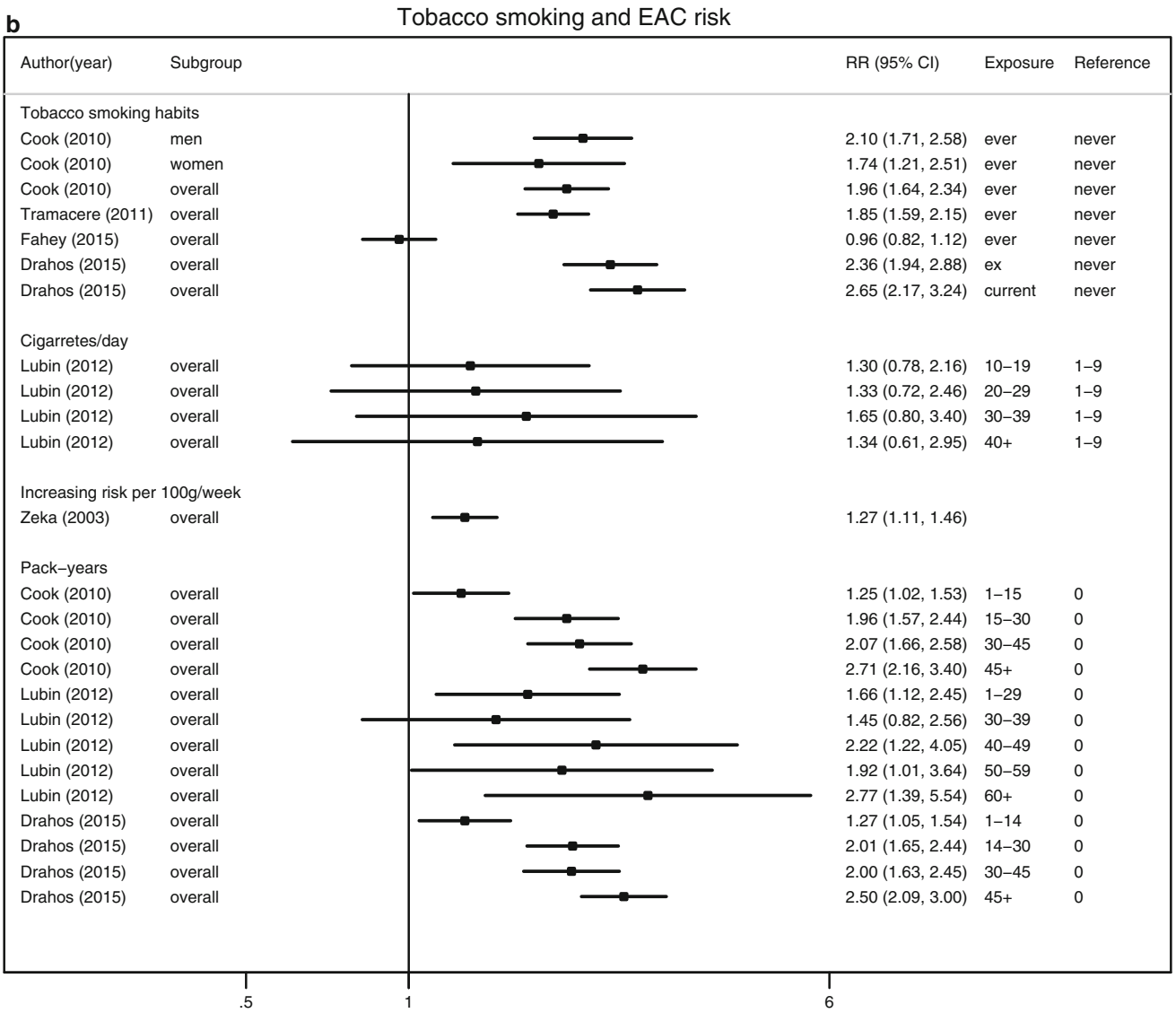

Fig. 3 continued

HPV infection

Seven studies focused on the association between HPV infection and the occurrence of ESCC [55–61], while one other did not provide histology-specific estimates [62]. A positive association between HPV infection and ESCC was reported in all studies, with overall RRs ranging between 2.69 [55] and 3.32 [56]. However, results varied according to geographical areas (no significant associations found for Europe and America [55, 56, 61], while a significantly increased risk of ESCC was reported in Asia, with RRs of approximately 4 being reported for China [57, 58]) and HPV subtype (HPV-16 was consistently reported as being associated with ESCC, contrarily to HPV-18 and other subtypes [60]).

BMI and central adiposity

Twelve publications assessed the effects of BMI on EC (Supplementary Fig. S3), one of which did not provide histology-specific RRs [63]. ESCC was focused on by four meta-analyses [22, 27, 64, 65]. A study found no significant change in ESCC risk with an increment of 1 kg/m^2 [22], while another described a significant reduction with an increment of 5 kg/m^2 (RR = 0.71 for men and RR = 0.57 for women) [64]. A meta-analysis published in 2015 found a significantly reduced ESCC risk among individuals with a BMI over 25 (RR = 0.8, 95% CI 0.67, 0.95), but not among obese individuals (RR = 1.05, 95% CI 0.76, 1.46), when compared to those with a normal weight [27].

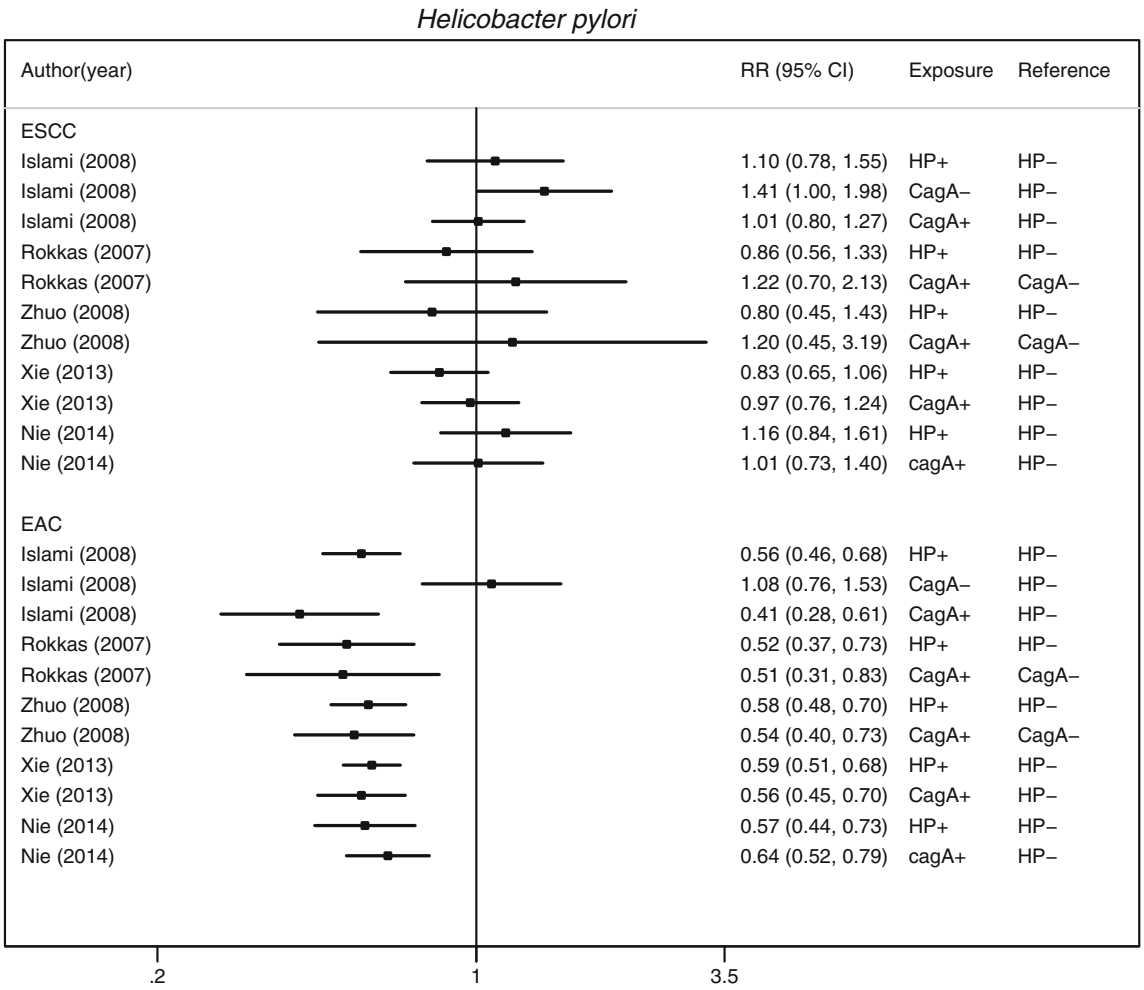

Fig. 4 Forest plot of overall association between *Helicobacter pylori* infection and the occurrence of esophageal cancer, by histological subtype. *RR* relative risk, *CI* confidence interval, *ESCC* esophageal squamous cell carcinoma, *EAC* esophageal adenocarcinoma

EAC was focused on by 11 meta-analyses, eight of which reported a significant dose–response effect of BMI [22, 34, 64–69]. EAC risk was found increasing by 13% per 5 kg/m^2 (RR = 1.13, 95% CI 1.11, 1.16) [69], while non-significant associations were found when comparing obese with normal weight men (RR = 1.23, 95% CI 0.58, 2.60) [70]. When comparing the highest with the lowest categories of central adiposity, an RR of 2.51 (95% CI 1.56, 4.04) was reported [71].

Physical activity

Five meta-analyses focused on the association between physical activity and EC [27, 72–75], one of which did not provide histology-specific estimates [74]. The remaining four meta-analyses compared the highest with the lowest levels of exercise, finding no significant association with ESCC [27, 72, 73, 75]. Two found a significant protective effect of physical activity on EAC risk (RR = 0.79 [72] and RR = 0.68 [75]), while the other two found no significant association [27, 73].

Further stratified results were only available for EC as a whole. A significantly reduced risk of EC was reported for studies from North America (RR = 0.77, 95% CI 0.64, 0.92), Australia (RR = 0.72, 95% CI 0.57, 0.91), and the Middle East (RR = 0.48, 95% CI 0.29, 0.81) [72], but not from Europe or Asia [72, 73, 75]. A reduced risk of EC was also reported by sex, and in both case–control and cohort studies [72, 73, 75].

Diet

The effects of some dietary aspects were only reported for EC as a whole: while no significant association was described with energy intake [76], barbecued meat [77], eggs [22], milk and dairy products [22], and black tea [78] consumption, protective effects were found regarding citrus fruits [22], raw and non-starchy vegetables [22],

lutein and zeaxanthin intake [79]. For the remaining diet-related factors, 12 meta-analyses did not report histology-specific results [17, 22, 76, 80–88].

Among meta-analysis addressing histologic type-specific data, ESCC risk was significantly lower among individuals presenting a "healthy dietary pattern" (higher loading of fruits, fresh vegetables, dietary fiber and antioxidants and a lower loading of fat dairy, processed food and meat) (RR = 0.36) and higher for a "drinker/alcohol dietary pattern" (higher loading of wines, beers, and spirits) (RR = 2.34), while it did not significantly change for a "Western dietary pattern" [89]. When comparing the highest with the lowest levels of intake, no significant associations were found for ESCC with dietary glycemic index [90, 91] or consumption of meat (overall [77, 92] and among women [93]), barbecue [93], cereals [93], fat (among women) [93], fiber [95], salt (among women) [93], acrylamide [85, 96], zinc [97], beta-carotene [79], green tea [78], coffee [78, 93, 98], coffee with milk [93], or soft drinks [99]. A significantly increased ESCC risk was found with the consumption of pickled vegetables (RR = 2.08) [100], meat (RR = 1.46 among men) [93], red meat (RRs between 1.55 and 1.86) [77, 92, 101, 102], fat (RR = 1.57 among men) [93], salt (RR = 2.11 among men) [93], maté (RR = 1.34 among men, RR = 2.20 among women) [93, 94] and regarding the temperature at which foods and beverages were consumed (RR = 1.6) [103], while a significantly decreasing ESCC risk was reported for fruit and vegetables (RRs between 0.4 and 0.6, with marked differences between sexes and geographical regions, see Supplementary Fig. S4) [93, 104], white meat (RR = 0.63) [92], folate (RR ≈ 0.65) [105, 106], alpha-carotene (RR = 0.82) [79], beta-cryptoxanthin (RR = 0.83) [79], lycopene (RR = 0.74) [79] and tea (RR = 0.53 among men) [93]. For poultry [77, 92], fish [77, 92, 107], processed meat [77, 92, 101, 102], and glycemic load [91], results were inconsistent between meta-analyses. When evaluating dose–response effects, increments of 100 g/day in consumption were found to decrease ESCC risk by nearly 40 and 60%, for fruit and vegetables, respectively [104], and increasing ESCC risk by 41% for red meat [102].

For EAC, when comparing the highest with the lowest levels of intake, no significant associations were found with the consumption of poultry [77, 92], white meat [92], fish [77, 92, 107], acrylamide [85, 96], zinc [97], vitamin E [108], coffee [78, 98], soft drinks [99] and the temperature at which foods and beverages were consumed [103], while a decreasing risk was found regarding folate (RR ≈ 0.5) [105, 106], fiber (RR = 0.66) [95], beta-carotene (RR = 0.46) [79, 108] and vitamin C intake (RR = 0.49) [108] and an increasing risk was reported with the consumption of total meat (RR = 1.96) [92], red meat (RR between 1.2 and 1.4) [77, 92, 101, 109] and processed meat (RR ≈ 1.4) [77, 92, 101, 109]. Increments of 100 g/day in consumption were found to decrease EAC risk by 13 and 9%, for fruit and vegetables, respectively [110], and to increase EAC risk by 45% for red meat [102].

Interactions between risk factors

Seven studies evaluated the interaction between some of the aforementioned risk factors for EC, EAC, or ESCC [4, 17, 25, 36, 48, 67, 93].

For ESCC, significant interactions were found between areca nut chewing and tobacco smoking [48], tobacco smoking and alcohol drinking [4], and between the consumption of maté at very hot temperatures and drinking more than 1.5 l of maté per day [93].

Ishikawa et al. [17] evaluated the potential effect modifications of smoking (current), alcohol (daily), and green tea (≥3 cups/day) consumption on EC risk, by analyzing combined categories of these variables and using people with none of the exposures as reference. The interactions between smoking and alcohol drinking, smoking and green tea consumption, alcohol and green tea consumption, and all three variables yielded RRs of 9.23 (95% CI 2.10, 40.60), 4.99 (95% CI 1.11, 22.43), 2.97 (95% CI 0.53, 16.58) and 11.10 (95% CI 2.63, 46.51), respectively. Ansary-Moghaddam et al. [36] found a significant interaction between smoking and alcohol for the occurrence of EC.

Discussion

The association between the most well-known risk factors for esophageal cancer and its occurrence have been extensively described in the literature and an increasing number of meta-analyses have been published focusing on those determinants. Although methodological limitations are inherent to the primary studies included in the meta-analyses, this review depicts the state-of-the-art on the modifiable risk factors for EC, showing marked differences between its subtypes regarding the strength of association with each determinant. In most situations, risk estimates did not differ significantly between meta-analyses focusing on the same risk factors, but there were some exceptions that should be discussed.

Most meta-analyses found no significant association between alcohol drinking and EAC, even at high levels of consumption. However, two meta-analyses, originated from pooled analysis of studies included in the International Barrett's and Esophageal Adenocarcinoma Consortium (BEACON), suggested a protective effect of low/moderate alcohol consumption on EAC risk [28, 34].

The authors argued that these results could depict a true association, as alcohol consumption may have favorable effects on insulin resistance or levels of serum lipids and lipoproteins [111], which may be important for EAC risk. In 2015, two meta-analyses compared ever with never drinkers: while Drahos et al. [34] found a significant protective effect of alcohol consumption on EAC risk, at all ages and in people aged 70 or older; Fahey et al. [27] found no significant association. Although results obtained by Fahey et al. were based on a systematic review, only two case–control studies (from Sweden and the USA) were used to obtain the summary estimates, while Drahos et al. used individual data from eight BEACON case–control studies (from Australia, Ireland, Sweden, and the USA). Therefore, results provided by the latter are more reliable, since a larger number of studies were included in the analysis, and the use of individual data allows for the adjustment of each study's results to the same variables, ensuring the comparability of results.

Tobacco consumption was found to increase the risk of EAC in all meta-analyses, with the exception of Fahey et al. [27], who reported no significant association. As before, this lack of association is probably due to the smaller number of studies included in the meta-analysis, in comparison with the other studies performing similar evaluations [34, 38, 41].

Our study has shown that a significant reduction in ESCC risk could be obtained from alcohol drinking and tobacco smoking cessation, with RRs reaching similar values to the ones observed in individuals who never drank or smoked, within some years after cessation. This depicts the importance of planning interventions aimed to reduce the consumption of both alcohol and tobacco. Future studies focusing on EAC to provide such estimates would also be useful, especially given the marked increase in EAC incidence trends observed in Western countries in the last decades [1, 112]. Two meta-analyses [72, 75] found an inverse association between physical activity and EAC risk, while two others [27, 73] found no significant association. Those not showing a significant result were the ones including the smaller number of studies in the analyses.

In all meta-analyses identified in our study, HP infection was consistently described as having a protective effect of EAC risk, while no significant association was found with ESCC. The mechanisms underlying the inverse association between HP infection and EAC are not clear, but it has been suggested that hypoacidity in association with gastric atrophy may have a role [113].

Overweight and obesity were consistently reported as risk factors for EAC, but a protective effect of BMI for ESCC was also observed. A possible explanation for this inverse association is a negative confounding of the BMI and cancer association by smoking intensity [114], which has been supported by studies presenting an inverse association between BMI and ESCC risk among smokers, but not among non-smokers [115].

Although our quality assessment has shown that most meta-analyses published are of good quality, the key limitation on the interpretability of our findings is the heterogeneity between (and within each of) the meta-analyses selected for inclusion in our review. Among the 81 studies performing a systematic review of literature, some focused on a specific geographical area (e.g., Japan [20, 40]) or included only studies of a given design (e.g., cohort studies [83, 88]); six of the 12 studies obtained through pooled analyses used data from BEACON, three used data from studies conducted in South America, two in Asia, and one in Italy. Thus, cultural aspects, customs, and lifestyles of each geographical area are likely explanations for the differences found between summary estimates provided for some determinants, namely regarding diet.

Furthermore, moderate-to-high degrees of heterogeneity were observed in several meta-analyses, with many authors mentioning the difficulties in using available data from observational studies, since there is no standardization in data collection and reporting [27, 114].

Our inclusion criteria focused on environmental risk factors, leading to the exclusion of many studies focusing on pharmacological treatments (e.g., nonsteroidal anti-inflammatory drugs) and genetic factors. However, some of the latter are widely recognized as significantly associated with the risk of EC, and therefore their role cannot be disregarded. For example, the biologic effects of alcohol intake on EC depend on the individuals' genotype. Subjects with the ALDH2 (aldehyde dehydrogenase 2) Lys487 allele have a deficiency of ALDH2, leading to a higher risk of EC than that observed in individuals with no deficiency and consuming the same amount of alcohol [116]. GERD and Barrett's esophagus are among the most commonly mentioned risk factors for EAC in epidemiological studies, but they were also excluded from the present study, as it is arguable whether they are modifiable factors. Few meta-analyses have focused on these determinants, mainly due to the high heterogeneity found between individual studies included in existing systematic reviews. Nevertheless, the existing meta-analyses reported a gradually increased risk of EAC with the increasing frequency and duration of GERD symptoms [34, 117, 118]. There are some comorbidities that have also been assessed through meta-analyses and may be worth analyzing in future studies. Examples include an increased risk of ESCC found in people with gastric atrophy (RR = 1.94, 95% CI 1.48, 2.55) [119] and an increased risk of EAC in the presence of diabetes mellitus (RR = 2.12, 95% CI 1.01, 4.46) [120].

In conclusion, this comprehensive systematic review summarizes the state-of-the-art on the etiology of EC, showing evident differences between ESCC and EAC regarding some risk factors. This reinforces the importance of a separate assessment of EC subtypes to allow for a proper discussion of incidence trends and a suitable planning of interventions towards the reduction of cancer burden in the population.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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