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Review

Lifestyle, WCRF/AICR Recommendations and Esophageal Adenocarcinoma Risk. A Systematic Review of the Literature

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Abstract: One of the most notable changes in the Esophageal Cancer (EC) epidemiology is the rising incidence and prevalence of esophageal adenocarcinoma (EAC) in developed countries, likely due to lifestyle and/or environmental factors that may play an important role in EAC onset. The aim of this systematic review was to collect and summarize all the available evidence regarding lifestyle, diet and EAC risk. We searched the PubMed and Scopus databases in January 2021 for studies providing information about lifestyle, diet, WCRF/AICR recommendations and EAC risk. A total of 106 publications met the inclusion criteria. Body mass index (BMI) and waist circumference (WC) are associated with increased EAC risk. Physical activity does not appear to have a significant direct role in EAC risk. A diet rich in fruit, vegetables, and whole grains appeared to be more protective than a diet rich in animal fat, red meat, and processed meat. Alcohol does not seem to be related to EAC whereas smokers, particularly heavy smokers, have an increased risk of EAC. Primary prevention remains the best option to avert EAC. BMI and WC, along with low consumption of red and processed meat, high consumption of plant food, and the avoidance of smoking are pivotal for EAC prevention.

Keywords: lifestyle, esophageal cancer, cancer prevention, esophageal adenocarcinoma

1. Introduction

Esophageal cancer (EC), including squamous cell carcinoma (ESCC) and adenocarcinoma (EAC), is the sixth leading cause of cancer-related death (mortality rates 7.7 per 100,000) both in men and women worldwide, and the eighth most common cancer with approximately 604,100 new cases occurring in 2020 [1, 2]. While the incidence of many types of cancer is expected to decrease over the next few decades, it is estimated that by 2040, esophageal cancer will increase by 63.5% [3]. One of the most notable changes in the epidemiology of esophageal cancer lies in the rising incidence and prevalence of EAC over the last decades in developed countries (e.g. the United Kingdom, Australia, the Netherlands, and the USA) [4, 1]. The higher incidence of EAC is recorded in males more than in females (the male-to-female incidence ratio is 4.4:1 for EAC) [5], and in Caucasians with a high socioeconomic status [1, 6, 7].

Given the rapid increase in the overall incidence rate and the variation in the change in rates among different geographic areas, it is likely that lifestyle and/or environmental factors, as well as genetic factors, play important roles in the development of esophageal adenocarcinoma [8]. In 2007, the World Cancer Research Fund and the American Institute for Cancer Research (WCRF-AICR) proposed a series of recommendations concerning the correct lifestyle approach to reduce the risk of cancer. In particular, these recommendations highlighted the importance of body weight control, physical activity, vegetable and fruit consumption, and limited intake of animal source foods, salty foods, alcohol, and

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nutritional supplements [9]. In their report, the WCRF/AICR indicated that the intake of fruit, non-starchy vegetables, β-carotene, and vitamins C and E was deemed "probably" protective against the risk of esophageal cancer, while the evidence linking fiber and folate intake to lower disease risk was described as "limited" [9]. The report also indicated that consumption of red meat and processed meat "probably" increases disease risk, while no food or nutrients were considered to have "convincing" evidence of an association with esophageal cancer. Unfortunately, the 2007 WCRF/AICR report did not discriminate between the two common histological types of esophageal cancers (squamous cell carcinoma and adenocarcinoma), even though these two malignancies have substantially different risk factors and etiology. In fact, the esophageal cancer section was updated in 2018 as part of the WCRF/AICR 2018 Continuous Update Project (CUP) Expert Report [10], differentiating between EAC and ESCC. However, in this report, body fat (marked by body mass index [BMI], waist circumference, and waist-hip ratio) was confirmed as a risk factor with convincing evidence for EAC. No protective factors with convincing or probable evidence are mentioned in the report. "Limited-suggestive" evidence in decreasing EAC risk is provided for vegetables and physical activity. On the contrary, no conclusive evidence was found regarding all other dietary and lifestyle factors, such as dietary fiber intake, and fruit and vegetable consumption [10]. Nevertheless, it should be considered that, due to the possible interaction between different foods and micronutrients, or the protective/causative role of other lifestyle habits, it is quite difficult to identify the real association between specific food components and EAC. It should also be taken into account that the 2018 CUP Expert Report was based on a 2016 literature review.

The aim of the present systematic review was primarily to collect and summarize all the available evidence concerning diet and other potential EAC risk factors and, secondly, to assess any potential new evidence.

2. Materials and Methods

2.1 Search strategy

Two Authors (DN, VG) independently performed a systematic search of published articles using the PubMed and Scopus databases up to January 2021. The search strategy was based on three parameters: esophageal adenocarcinoma, life styles, and study design. We used the following search terms combined with Boolean operators: (((((("Surveys and Questionnaires"[Mesh] OR "Cross-Sectional Studies"[Mesh]) OR "Cohort Studies"[Mesh]) OR "Case-Control Studies"[Mesh]) OR "Interview" [Publication Type] OR "population based" OR "food frequency questionnaire" OR FFQ)) AND ((((((((("Fruit"[Mesh]) OR ("Vegetables"[Mesh] OR "Vegetable Products"[Mesh])) OR "Body Mass Index"[Mesh]) OR "Diet"[Mesh]) OR "Social Class"[Mesh]) OR "Tobacco Use"[Mesh]) OR "Smoking"[Mesh]) OR "Alcohol Drinking"[Mesh])) AND ("Adenocarcinoma Of Esophagus" [Supplementary Concept] OR "Esophageal Neoplasms"[Mesh:NoExp])). Both medical subject headings (MeSH) and free-text search terms were applied in order to maximize the citation search. No time limitation was applied. We also reviewed the reference lists from retrieved articles and those from previous review studies to identify additional relevant studies that may not have been identified by our database searches. Article screening for this systematic review was carried out manually and with the EndNote®6.0.1 (Thomson Reuters) software. The selection process was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guideline [11]. The review protocol was registered on PROSPERO [12], the International Prospective Register of Systematic Reviews funded by the National Institute of Health Research (ID number: CRD-42021228762 at https://www.crd.york.ac.uk/prospero/, accessed on 5 January 2021 and formally registered on 5 February 2021).

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2.2 Inclusion and exclusion criteria

The rationale for the selection of inclusion/exclusion criteria was based on the PICOS framework [13]. This systematic review only includes articles in the English language, full length, carried out on adult humans (studies using animal or in vitro models were excluded), and those focusing on EAC. Epidemiological studies of any design (case-control, cross-sectional or cohort studies evaluating the relationship between diet, BMI, lifestyle, and the risk of EAC) were included. Experimental animal models, genetic or immune-histochemical studies, and studies evaluating a combination of EAC and ESCC or EAC and gastric adenocarcinoma or EAC and gastric cardia adenocarcinoma were also excluded. Inclusion/exclusion criteria are presented in Table 1. Abstracts, case reports, letters, comments, reviews, and studies without appropriate data for extraction were excluded.

Table 1. Inclusion and exclusion criteria for the studies' review combining the PICOS framework

Parameter	Inclusion	Exclusion
Population	Adult population, Male and Female, Focusing on EAC alone.	Population with ESCC and EAC combined, esophageal and gastric cardia adenocarcinoma combined, only considered ESCC
Intervention	Administration of questionnaire evaluating, food frequency, dietary pattern, BMI, physical activity, smoking habit, alcohol consumption, socio-demographic characteristics	Medication or other intervention intended to reduce EAC risk
Control/ Comparison	Stratification according to dietary habits, dietary pattern, BMI, physical activity, smoking habit, alcohol consumption, socio-demographic characteristics	None
Outcomes	Risk of EAC	Risk of EAC and ESCC combined or ESCC alone. Risk of EAC and gastric cardia adenocarcinoma combined.
Study design	Epidemiologic studies (case-control, cross-sectional or cohort studies), pooled analysis, meta-analysis.	review article, expert opinion, commentary, article with no quantitative information or details, experimental animal models, genetic or immune-histochemical studies
Language filter	Only article in English language	Any other language
Time filter	From inception until May 2016	None

Abbreviations: EAC, Esophageal Adenocarcinoma; ESCC, Esophageal Squamous Cells Carcinoma; BMI, Body Mass Index

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2.3 Data extraction and quality evaluation

The data below was independently extracted from each study by two authors (DN and VG). Discrepancies and missing data were resolved by group discussion and the opinions of other researchers were sought for further discussion (SR) in the case of any remaining discrepancies. As performed in previous published reviews[14-16], data were tabulated on a standardized and pre-piloted data extraction form, and elaborated in Microsoft Excel® 2013 for Windows (Microsoft Corporation, Redmond, Washington, US). The following data were extracted: the first author's last name, the publication year, the study period, the country where the study was conducted, the study design (case-control, cohort, and cross-sectional), the number of cases and controls or the cohort size, the study aim, data extraction and, lastly, the results obtained in relation to EAC risk. The characteristics of included studies are presented in Tables which are stratified by study design. The quality of the included publications was assessed by two independent authors (AM and CF) using the New-Ottawa Scale (NOS) for observational studies and stratified by study design [17]. The NOS provides a checklist for case-control and cohort studies, but not for cross-sectional ones. For this reason, we used an adapted NOS for cohort studies in order to perform a quality assessment of cross-sectional studies, which is available in the literature [18]. As in previous systematic reviews, scores of 0–3, 4–6, and 7–9 were rated low, moderate, and high quality, respectively [19-21]. With regard to item 7 of the NOS checklist for cohort studies, we determined that a 10-year follow-up period was acceptable for the occurrence of outcome of interest [22].

3. Results

3.1. Literature search and quality evaluation

Our search strategy yielded 1,240 articles. Among these, 1,233 were found through an electronic literature search in the databases and 7 additional articles were found as references in the retrieved articles. These included 77 articles which were removed because they were duplicates, 46 articles removed because they were not in English, 75 were reviews, 648 were excluded because the topic was unrelated, 106 referred to Barrett's esophagus, 173 were about ESCC, and 1 was an editorial. A further 8 publications were excluded because data did not specifically refer to EAC, but rather a combination of EAC with squamous esophageal cancer or esophagogastric junction [23-30]. A final number of 106 publications were included in the systematic review. The selection process is depicted in Figure 1. Results are presented and grouped in accordance with the WCRF/AICR 2018 recommendations for cancer prevention [10]. The main characteristics of included studies are reported in Table 2 for case-control studies (n= 66) [31-96] and Table 3 for cohort (n= 39) and cross-sectional studies (n= 1) [97-136].

Based on defined cut-points, more than half of the case-control studies were deemed high quality (n= 39/66, 59.1%) however, the rest contained a risk of bias. In fact, medium quality was assigned to 39.4% of studies (n= 26/66) and low quality to 1.5% of studies (n= 1/66). The main concerns were associated with the definition of controls (item 4) not described in approximately 3 out of 4 studies (n=18/66), the non-response rate (item 8) not described in 22.7% of the studies (n= 14/66), and a difference between cases and controls in half of the studies (33/66). Less than half the studies (n= 27/66, 40.9%) also had a satisfactory ascertainment of exposure (item 6), with "interview not blinded to case-control status" being the most common outcome in those studies which did not collect a positive score. To the contrary, practically all cohort studies were rated as high quality (n= 38/39, 97.4%), while the remaining one was rated as medium quality, achieving a score of 6 points. Information regarding lost to follow-up (item 8) was not stated in 20.5% of studies (n= 8/39), representing a potential risk of both information and selection bias. Another critical item was the follow-up length (item 7), which was found to be insufficient for outcome to occur in approximately one-fourth of the studies (n= 10/39). With regard to the ascertainment of exposure (item 3), 23% of the studies (n= 9/39) used a written self-re-

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ported questionnaire, which is at risk of potential recall and social desirability bias. Furthermore, 25.6% (n= 10/39) did not ascertain that EAC was absent at the beginning of the study. Lastly, a single cross-sectional study [103], deemed high quality (7 points), was included. Supplementary Table S1 reports the quality assessment of case-control studies, Supplementary Table S2 reports the quality assessment of cohort studies.

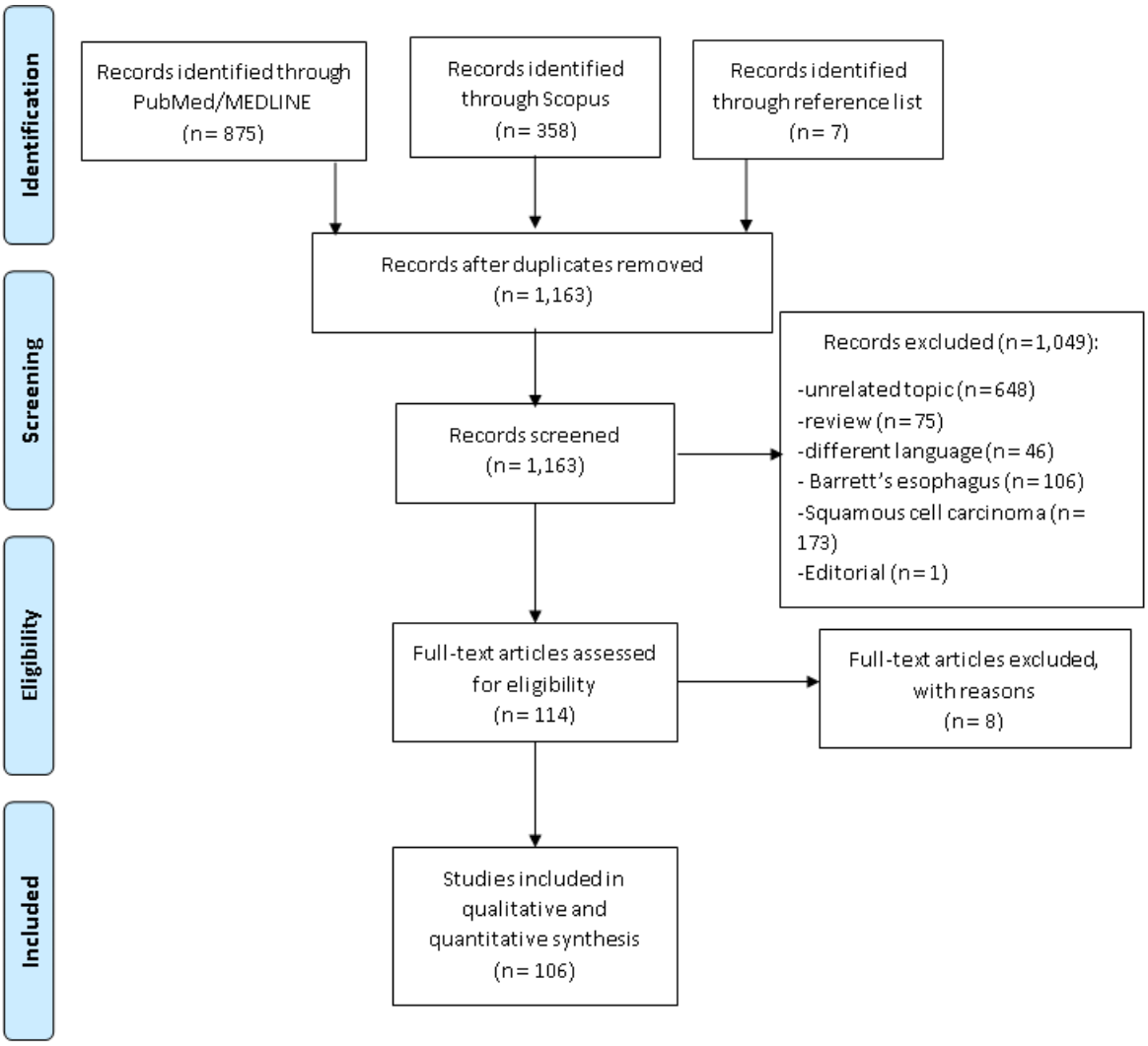

Figure 1. Flowchart depicting the studies' selection process (PRISMA flow diagram).

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Table 2 Characteristics of included case-control studies, in alphabetical order

Author year [Ref]	Study period	Study design	EAC Cases (n)	Control (n)	Aims	Data	Main Results
Anderson et al. 2009 [31]	2002-2004 IE	Population-based case-control	227	260	To investigate relationship between alcohol intake and EAC.	Structured computerized interview	No association between total alcohol consumption and EAC.
Anderson et al. 2007 [32]	2002-2004 IE	Population-based case-control	227	260	To investigate risk factors associated with EAC.	Structured interview	Waist-hip ratio was measured at the time of interview, and no relationship was observed between waist-hip ratio and EAC. Compared to controls, EAC patients had a lower intake of fruit, but not vegetables. Strong relationship between smoking and EAC.
Bahmanyar et al. 2006 [33]	1995-1997 SE	Case-control	185	815	To examine the association of dietary patterns and the development of EAC.	Structured FFQ, including 63 food and beverage items of interest evaluating 20 y before interview.	The healthy diet pattern was, in general, associated with moderately reduced risks, non-statistically significant.
Bollschweiler et al. 2002 [34]	1997-2000 DE	Pilot-study	47	50	To analyze the influence of daily vitamin consumption on the frequency of EAC.	Structured questionnaire	EAC risk reduction with an intake of 13mg/day of vitamin E (RR=0.013, 95% CI=0.1-0.5, p=0.0004) *and* >100mg/day of vitamin C (RR=0.33, 95% CI= 0.11-0.92, p=0.034).
Chen et al. 2002 [35]	1992-1994 US	Population-based case-control	124	449	To investigate the relationship between nutrient intake and EAC.	Telephone interview. Short Health Habits and History Questionnaire.	Significant inverse association with EAC risk and vitamin A, β-cryptoxanthin, riboflavin, folate, zinc, dietary fiber, protein, and carbohydrate. Positive association between saturated fat intake and risk of EAC.
	1992-1994		124	449			

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Chen et al. 2002 [36]	US	Population-based case-control			To evaluate potential roles of dietary patterns in the etiology of EAC.	Telephone interviews. Short Health Habits and History Questionnaire.	Risk of EAC was inversely associated with intake of dairy products, fish, all vegetables, citrus fruits and juice, and dark bread and was positively associated with gravy intake.
Chen et al. 2011 [37]	2002-2006 CN	Case-control	98	294	Relation between smoking and alcohol consumption and EAC risk.	Interview survey	Heavy alcohol consumption increases risk of EAC independent of the duration.
Cheng et al. 2000 [38]	1993-1996 UK	Population-based case-control	74	74	Relation between fruit and vegetables intake, BMI and breast feeding and EAC risk.	Dietary questionnaire for recent diet (3 years before) and for past diet (30 year before).	Statistically significant inverse relation between fruit intake and EAC risk. Statistically significant positive association between higher BMI and risk of EAC.
Chow et al. 1998 [39]	1993-1995 US	Case-control	292	695	To evaluate the possible role of excess weight as a risk factor for EAC.	Structured interview to elicit information up to 1 year prior to diagnosis for case patients and date of interview for control subjects.	Stratification by usual BMI showed excess risks associated with weight gain greater than or equal to 46 lbs. Positive association between risk of EAC and usual BMI was significantly ($p = 0.030$) modified by age. Largest BMI-related increase in risk was found among non-smokers, followed by current smokers and then former smokers.
Corley et al. 2008 [40]	2006 US	Nested case-control	101	2,800	To assess the association between abdominal obesity, BMI, and the risk of EAC.	Instructed examiner collected anthropometric data. Questionnaire regarding potential confounders such as GERD symptoms within the last 6 months, food intake, drug use (aspirin, antacid, pain medications) hiatal hernia diagnosis, smoking status, recent alcohol use, race.	Abdominal diameter is an independent risk factor, even after adjustment for BMI, suggesting that the association between abdominal diameter and cancer risk was not solely mediated through a higher BMI increasing abdominal diameter.

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Dai et al. 2016 [41]	2002-2005 IE	Population-based case-control	218	252	To evaluate the association between Mg intake and EAC risk.	Trained interviewers using an electronic questionnaire investigating lifestyle, medication, and co-morbidities. Dietary intake was assessed using a 101-item FFQ, adapted from a version of the EPIC-FFQ.	No significant association between intake of Mg and risk for EAC or a significant interaction between intakes of vitamin D and Mg.
de Jonge et al. 2006 [42]	2003-2005 NL	Hospital-based case-control	91	244	To identify risk factors to differentiate between Barrett's Esophagus patients with low or high risk of EAC.	Non-validated questionnaire.	Tobacco smoking and BMI >25 Kg/m^2 increased the risk of EAC.
Drahos et al. 2016 [43]	1992-2012 UK	Population-based case-control	592	2,901	To investigate MetS in relation to EAC.	GPRD	No association between MetS and risk of EAC.
Duan et al. 2009 [44]	1992-1997 US	Population-based case-control	220	1,356	Relation between passive smoking and risk of EAC.	In-person interview with structured questionnaire.	Current smokers were at increased EAC risk. Never smokers exposed to passive smoking during childhood were not at increased risk of EAC. Exposure to at least one smoker during adulthood was associated with an elevated risk of EAC.
Engel et al. 2003 [45]	1993-1995 US	Population-based case-control	293	695	To identify population attributable risk (PAR) for EAC.	Trained interviewers administered structured, in-person interviews; FFQ; Blood samples.	Decreased risk of EAC compared to increasing levels of education or income. Risk of EAC was double in current smokers compared to never smokers. No association between EAC and alcohol consumption (beer and hard liquor). Wine drinking was also associated with a decreased risk of EAC.

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Gammon et al. 1997 [46]	1993-1995 US	Multicenter case-control	293	695	To identify EAC risk factors.	Face-to-face interviews with structured questionnaire.	Doubled risk of EAC among current and former smokers. No association between beer and hard liquor intake. 40% risk reduction was associated with wine drinking.
Gao et al. 1994 [47]	1990-1993 CN	Case-control	51	1,552	Relation between alcohol consumption, smoking habit and risk of EAC.	Structured standardized questionnaire.	Smoking more than 30 cig/day was associated with an increased risk of EAC. Alcohol did not increase EAC risk.
Garidou et al. 1996 [48]	1989-1991 GR	Case-control	56	200	Relation between lifestyle and EAC risk.	Structured standardized questionnaire; FFQ.	Higher education (≥12 y) was associated with a decreased risk of EAC. Smoking more than 1 pack of cigarettes/day was a risk factor for EAC. Alcohol consumption >5 drinks/day was a risk factor for EAC. Hot or very hot beverages were associated with a higher risk of EAC compared to cold drinks. Coffee drinks were not associated with EAC risk. Chronic intake of analgesics did not increase EAC risk.
Hashibe et al. 2007 [49]	2000-2002 RO, RU, CZ, PL	Multicenter case-control	35	1,114	Relation between cigarette smoking, alcohol intake and risk of EAC	Face-to-face interview with structured questionnaire.	No statistical association between cigarette smoking and EAC, also considering frequency and duration of smoking habit. The same results also apply to alcohol consumption.
Ibiebele et al. 2012 [50]	2002-2005 AU	Population-based case–control	299	1,507	To investigate the role of dietary patterns in EAC risk.	Self-administered questionnaire (general data); 139-item semi-quantitative FFQ.	Meat-and-fat dietary pattern had a 2-fold increased risk of EAC. High-fat dairy foods appeared to play a dominant role in the association between the meat-and-fat pattern and risk of EAC.
Ibiebele et al. 2013 [51]	2002-2005 AU	Population-based case–control	299	1,507	Relation between dietary	135-item semi-quantitative FFQ.	Inverse association between vitamin E intake and EAC and high antioxidant score.

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					antioxidant intake and risk of EAC.		
Jansson et al. 2005 [52]	1995-1997 SE	Population-based case-control	189	820	To examine the association between socioeconomic status and development of EAC.	Questionnaire to collect data on occupational history, educational level and other socioeconomic dimensions.	Low socioeconomic status increased EAC risk. However, the association is not statistically significant in the adjusted model.
Lagergren et al. 1999 [53]	1995-1997 SE	Population-based case-control	189	820	To examine the association between BMI and EAC.	Face-to-face interview.	The association between BMI and EAC is highly significant.
Lagergren et al. 2000 [54]	1995-1997 SE	Population-based case-control	189	820	To examine the association between smoking, snuff, and alcohol use and development of EAC.	Face-to-face interview.	Weak or absent association between tobacco smoking and EAC risk.
Lagergren et al. 2006 [55]	1995-1997 SE	Population-based case-control	189	820	Association between carbonated drink intake and EAC.	Validated FFQ that surveyed intake of beverages and dietary patterns 20 years earlier.	No association between carbonated soft drinks or low-alcohol beer and EAC.
Lagergren et al. 2013 [56]	1995-1997 SE	Population-based case-control	189	820	Association between the proportions of carbohydrates, fat, and protein and the risk of EAC.	FFQ adapted from a validated standard questionnaire.	A high dietary proportion of carbohydrates decreased the risk of EAC, a high portion of fat increased the risk, while a high proportion of protein did not influence the risk of EAC.
Lahmann et al. 2014 [57]	1995-1997 SE	Population-based case-control	189	816	Relation between BMI and EAC.	Interview	BMI is a strong and independent risk factor for EAC.
	2002-2005	Population-based	299	1,507		135-item semi-quantitative FFQ.	GI, GL and total carbohydrate intake did not increase the risk of

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Lahmann et al. 2014 [58]	AU	case-control			Association between GI, GL, total carbohydrate intake and risk of EAC.		EAC. Strong inverse association between EAC risk and fiber intake.
Li, N. et al. 2017 [59]	1993-1195 US	Population-based case-control	500	2,027	Association between the intake of sweetened beverages and the risk of EAC.	104-item FFQ.	The intake of sweetened beverages is associated with an increased risk of EAC.
Lin et al. 2011 [60]	1994-1997 SE	Population-based case–control	189	820	Association between dietary acrylamide intake and risk of EAC.	FFQ concerning the habitual intake of 63 foods and beverages as recalled from 20 years before the interview.	No statistically significant associations were found. EAC risk moderately increased among persons with higher exposure to dietary acrylamide. Higher among overweight or obese subjects. No dose-response effects.
Lin et al. 2014 [61]	1995-1997 SE	Population-based case–control	181	806	To test whether dietary lignans, quercetin, and resveratrol synergistically decrease the risk of EAC.	FFQ concerning the habitual intake of 63 foods and beverages as recalled from 20 years before the interview.	Dietary pattern characterized by the intake of lignans, quercetin and resveratrol could have a protective role in the development of EAC.
Lin et al. 2012 [62]	1994-1997 SE	Population-based case–control	181	806	Association between dietary intake of lignans and risk of EAC.	Personal interview; FFQ with 63 foods and beverages, assessing dietary habits 20 y before the interview.	Reduction of EAC risk in subjects with a high dietary intake of lignans
Lindblad et al. 2005 [63]	1994-2001 UK	Prospective nested case-control	287	10	To prospectively assess the influence of BMI, tobacco, and alcohol on the occurrence of EAC.	Information recorded at least two years before the date when the tumor was first recorded or when the review revealed an earlier date of diagnosis.	People with BMI ≥25 kg/m^2 had an almost 70% increased risk of EAC with a statistically significant positive dose-response relation. Current smokers were at an increased risk of EAC. Female smokers were at a seemingly higher risk compared to men. Ex-smokers no increased risk

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							of EAC. Alcohol was not associated with risk of EAC.
Lu et al. 2016 [64]	1994-1997 SE	Population-based case–control	181	806	To assess the association between diet-related inflammation and EAC risk.	Face-to-face interview; FFQ with 63 foods and beverages, assessing dietary habits 20 y before the interview.	Significant positive associations between DII and EAC.
Massl et al. 2014 [65]	2003-2011 NL	Case-control	175	251	Relation between visceral adipose tissue measured by CT and EAC risk.	CT scan	Visceral adipose tissue is a risk factor in the development of EAC. Visceral adipose factor seems to be more important than obesity *per se*.
Mayne et al. 2001 [66]	1993-1995 US	Multicenter case-control	282	687	Associations between nutrient intake and risk of EAC.	Face-to-face interviews; 104-item FFQ.	Nutrients from plant foods (fiber, β-carotene, folate, vitamin C, and B6) were associated with a reduced risk of EAC. Nutrients from foods of animal origin (dietary cholesterol, animal protein, and vitamin B12) were associated with an increased risk of EAC
Mayne et al. 2006 [67]	1993-1995 US	Multicenter, population-based case -control	282	687	Association between CSD consumption and EAC.	In-person structured questionnaire asking about the frequency of "diet soft drinks or soda" and "regular soft drinks or soda", not diet consumption, 3 – 5 years before diagnosis (case) or interview (control).	High CSD consumption was associated with a similarly reduced risk of EAC in men and women (trend for women was not statistically significant). High consumption of diet CSDs as opposed to regular CSDs was associated with a statistically significant lower risk of EAC.
Mulholland et al. 2011 [68]	2002-2005 IE	Population based case-control	218	252	Association between vitamin D, Ca, and dairy product intake and the risk of EAC.	101-item EPIC-FFQ adapted for the Irish population; self-reported BMI.	A high vitamin D intake from foods is associated with elevated EAC risk but is unlikely to influence earlier stages of the carcinogenic pathway. Ca intake was not associated with EAC.
Murphy et al. 2010 [69]	2002- 2004	Case-control	224	256	Association between vitamin C,		The overall antioxidant index is associated with a lower risk of EAC.

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	IE				E, carotenoids, selenium, copper, and zinc and risk of EAC.	Interview; EPIC-FFQ adapted for the Irish population.	Vitamin C intake also reduces EAC risk in smokers. No association between carotenoids, vitamin E, zinc, and cooper and risk of EAC.
Navarro Silvera et al. 2014 [72]	1993- 1995 US	Multicenter population-based case-control	282	687	Relation between diet, lifestyle and EAC risk.	Structured in-person questionnaire; 104-item FFQ evaluating diet 3-5 years before EAC diagnosis or before the interview for controls.	Increased risk of EAC was associated with meat consumption. Reduced risk of EAC was associated with the consumption of non-citrus fruits.
Navarro Silvera et al. 2008 [70]	1993- 1995 US	Multicenter population-based case-control	282	687	Association between different food groups and risk of EAC.	Structured in-person questionnaire; 104-item FFQ evaluating diet 3-5 years before EAC diagnosis or before the interview for controls.	EAC risk was associated with a low intake of fruit, vegetables, and whole cereals. Fruits, and yellow and dark green vegetables are inversely associated with EAC risk. Red meat, dairy, and high-fat foods was associated with an inversed risk of EAC.
Navarro Silvera et al. 2011 [71]	1993- 1995 US	Multicenter population-based case-control	282	687	Relation between dietary patterns, lifestyle and EAC risk.	104-item structured in-person FFQ evaluating diet 3-5 years before EAC diagnosis or before the interview for controls.	Significant inverse association between the pattern of fruits/vegetables and EAC risk. Positive significant association between meat/nitrites and EAC.
O'Doherty et al. 2010 [73]	2002-2005 IE	Case-control	224	256	Relation between Iron intake and risk of EAC.	Structured computerized 101-item EPIC-FFQ, (adapted for the Irish population) relating to a period of 5 years before interview.	A low intake of non-heme iron and vitamin C was associated with EAC. Statistically significant inverse association between total iron intake. Heme iron was positively associated with EAC
O'Doherty et al. 2011 [74]	2002-2005 IE	Case-control	224	256	Association between dietary fat and meat intake with EAC.	Structured computerized 101-item EPIC-FFQ, (adapted for the Irish population) relating to a period of 5 years before interview.	Higher risk of EAC with high intakes of total fat, saturated fat, and monounsaturated fat. Higher risk of EAC with high consumption of fresh red meat.
Olsen et al. 2011 [75]	2002-2005	Population-based	364	1,580		Self-administered questionnaire	

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	AU	case-control			Population attributable fractions of EAC associated with BMI and smoking.		BMI≥30 and frequent acid reflux (≥1 time/week) accounted for the greatest proportions of EAC (23% and 36%, respectively). Total Population Attributable Fraction (PAF) associated with smoking, BMI, and symptoms of GERD was 76% (95% CI: 66, 84), and it was higher for men (78% v. 59% women), although the difference was not significant.
Pandeya N et al. 2008 [76]	2002-2005 AU	Population-based case-control	367	1,580	Association of duration, intensity, and smoking quantity with EAC.	A self-completed health and lifestyle questionnaire.	Ever smokers had a significantly higher EAC risk than never smokers. Duration of smoking was significantly associated with EAC, however, intensity was not. Time since quitting was independently associated with an approximate 15% risk reduction per decade.
Pandeya et al. 2009 [77]	2002-2005 AU	Population-based case-control	365	1,580	Relation between alcohol intake and EAC risk.	A self-completed health and lifestyle questionnaire.	No association between average weekly alcohol intake and EAC. No significant association between smoking and alcohol. EAC risk did not increase with beer intake. Subjects with a modest intake of wine had a significantly lower EAC risk.
Pandeya et al. 2010 [78]	2002-2005 AU	Population-based case-control	365	1,580	Relation between smoking and EAC risk in patients with GERD.	A self-completed health and lifestyle questionnaire.	GERD was associated with a 6.4-fold increase in EAC risk. Heavy smokers had a markedly high EAC risk.
Petrick et al. 2015 [79]	1993-1995 US	Multicenter population-based	274	662	Association between intakes of total flavonoids and lignans, and the incidence of EAC.	104-item face-to-face structured FFQ evaluating diet 3-5 years before EAC diagnosis or before the control interview.	Little or no consistent association was found between total flavonoid intake and the incidence of EAC. Intake of anthocyanidins was associated with a 57% reduction in the risk of EAC incidence. Anthocyanidins

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							were associated with a modestly decreased risk of mortality from EAC. ORs for isoflavones, for which coffee was the main source, increased for EAC.
Pohl et al. 2013 [80]	2005-2009 DE	Case-control	100	No-GERD (n=113) GERD (n=188)	To examine at what stage known risk factors exert their influence toward EAC progression.	Standardized questionnaire	Increasing BMI at age 40 showed a small, but significant, association with EAC. Consumption of 4 portions of fruits and vegetables per day showed a strong protective effect. Duration of smoking and timing of the largest meal during the day was not associated with EAC. Any history of smoking was associated with a 2.6-fold risk of EAC.
Ryan et al. 2006 [81]	1994-2004 IE	Prospective case-control	936	893	Relation between BMI and obesity and EAC risk.	Registered dietitian assessed every patient individually.	Males with a BMI>30 kg/m^2 had a higher risk of EAC than those with a BMI<22 kg/m^2. A high pre-illness BMI significantly raises the risk of EAC. Dose-dependent relationship between BMI and EAC in males.
Sharp et al. 2013 [82]	2002-2005 IE	Case-control matched study	223	223	Association between dietary folate and risk of EAC.	Structured interviews and completed food-frequency questionnaires.	EAC risk decreased with increasing folate intake. Vitamin B-6 intake was significantly inversely related to risks of EAC. Vitamin B-12 intake was positively associated with EAC.
Terry et al. 2000 [83]	1995-1997 SE	Nationwide, population-based case-control	185	815	Relation between vitamin C, β-carotene, and α-tocopherol intake and risk of EAC.	63-item FFQ in computer-aided face-to-face interviews. Usual intake 20y before the interview.	Vitamin C and β-carotene intake was inversely associated with the risk of EAC. α-tocopherol intake was not associated with EAC. Parallel dietary intake of vitamin C, Alpha-tocopherol, and β-carotene decrease the risk of EAC by about 50%. No risk reduction was associated with the intake of vitamin supplements for ≥3 years.

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Terry et al. 2001 [84]	1995-1997 SE	Nation-wide, population-based case-control	185	815	Association between fruit and vegetable consumption and the risk of EAC.	63-item FFQ in computer-aided face-to-face interviews. Usual intake 20y before the interview.	Individuals in the highest exposure quartile (median 4.8 servings/day) v. lowest (median 1.5 servings/day) have a 50% lower risk of EAC. There were no significant associations between any specific fruit or vegetable and EAC.
Terry et al. 2003 [85]	1995-1997 SE	Nation-wide, population-based case-control	185	815	Relation between heterocyclic amine intake and risk of EAC	63-item FFQ in computer-aided face-to-face interviews; usual intake 20y before the interview; questions on specific foods and cooking methods.	No association was found between heterocyclic amine intakes and the risk of EAC.
Thrift et al. 2014 [86]	BEAGESS (data from 14 epidemiological studies conducted in Western Europe, Australia, and North America)	Case-control Mendelian approach	999	2,169	To improve the precision of causal estimates between BMI and EAC.	Genetic data sourced from genome-wide association studies (GWAS).	EAC risk increased by 16% per BMI increase of 1 kg/m^2.
Tzonou et al. 1996 [87]	1989-1991 GR	Case-control	56	200	To identify dietary risk factors for EAC.	115-item validated semi-quantitative FFQ.	Added polyunsaturated fats are positively associated with EAC risk. Intake of vegetables, fruits, vitamin C, crude fiber, and vitamin A is inversely associated with EAC.
Veugelers et al. 2006 [88]	2001-2003 CA	Prospective hospital–based case-control	57	102	Relation between obesity, diet, smoking, and alcohol consumption and EAC risk.	102-point face- to- face interview; 150-item structured FFQ.	BMI was a statistically significant risk factor for EAC. Diets high in vitamin C were associated with a lower risk of EAC. Smoking significantly increases the risk of EAC Liquor consumption was not a statistically significant risk factor for EAC.
Vigen, C. et al. 2006 [89]	n.a.	Population-based case-control	212	1,330	Relation between occupational physical	In-person interviews and total lifetime occupational activity were calculated using	EAC risk decreases with an increase in the Total Activity Index (OR = 0.67, 95% CI = 0.38,1.19 for highest versus lowest quartile).

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					activity and EAC.	US Census job codes classified as sedentary, or moderately or highly physically active.	
Ward et al. 1997 [90]	1992-1994 US	Population-based case-control	137 whites only	502	Association between meat and gravy intake, meat cooking methods and doneness preference, and the risk of EAC.	Telephone interview; HHHQ	High intake of processed meats was associated with an elevated risk of EAC. The upper quartile of red meat intake was associated with about a 2-fold increased risk of EAC compared with the lowest quartile. Saturated fat, total fat, and protein intake were highly correlated with red meat intake. Consumption of gravy ≥4 times/week was associated with more than a 2-fold increased risk of EAC. Frying or broiling were not associated with risk of EAC. Among next-of-kin respondents, the ORs for barbecuing were 3.1 for EAC. Broiling/frying of pork and chicken was not associated with risk of EAC. Doneness preference was not strongly or monotonically associated with EAC overall.
Ward et al. 2012 [92]	1992-1994 US	Population-based case-control	124 whites only	449	Relation between heme and total iron intake from meat, and the risk of EAC using a new database of heme iron levels developed at the NCI.	Short HHHQ with addition of foods high in nitrate/nitrite and questions about meat cooking methods and doneness preferences for beef, pork, and chicken.	High intake of red meat was associated with a double increased risk of EAC (highest v. lowest quartile). The risk increased with increasing quartiles of heme and total iron from meat, with a stronger association for heme iron.
Ward et al. 2008 [91]	1992-1994 US	Population-based case-control	137	503	To assess the relationship between drinking water, nitrate	Questions about residential and water source history, demographic factors, to-	No association between intake of nitrate from public water and risk of EAC. Dietary nitrate and nitrite

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					and nitrite intake, and the risk of EAC.	bacco and alcohol use, pesticide use by farmers, occupational history medical conditions, and medication use. Short HHHQ with addition of foods high in nitrate/nitrite.	from animal food were significantly associated with EAC risk.
Whiteman et al. 2008 [93]	2001-2005 AU	Population-based case–control	367	1,580	To measure the relative risks of EAC associated with measures of obesity and their interactions with age, sex, GERD symptoms, and smoking.	Self-completed, mailed questionnaires; telephone interview.	Risks of EAC increased monotonically with BMI, with highest risk for BMI >40 kg/m^2. Risks associated with obesity were substantially higher among men and among those aged <50 years. Obese people with frequent symptoms of GERD had a significantly higher risk than obese people without reflux.
Wolfgarten et al. 2001 [94]	1997-1998 DE	Case-control	40	100	Relation between nutrient intake, dietary patterns and EAC risk.	2-page dietary questionnaire. Personal interview on nutritional habits using the EBIS computer program.	No significant differences between patients with EAC and controls regarding the intake of sodium, potassium, phosphate, zinc, and selenium. > 1,300 mg/day of calcium, > 500 mg/day of magnesium, and 18 mg/day of iron were inversely correlated with EAC. 90% of EAC patients had a higher intake of cholesterol and animal protein, and drunk more milk than controls. Dietary fiber was significantly higher in controls than in patients with EAC.
Wu et al 2007 [96]	1992-1997 US	Case-control	206	1,308	Relation between dietary fat and fiber intake and risk of EAC. To investigate risk associated with the intake	124-item food and beverage in-person interviews. Question on the use of dietary supplements also added.	EAC risk rose with increasing intake of total fat and saturated and monounsaturated fat, but was unrelated to the intake of polyunsaturated fat. High intake of total fiber was associated with a statistically significant 56% EAC risk reduction. Risk of

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					of total meat, red meat, poultry, fish/shellfish, and processed meat and EAC.		EAC was not significantly influenced by total meat or processed meat intake. Intake of poultry and fish/shellfish was unrelated to risk.
Wu et al. 2001 [95]	1992-1997 US	Large population-based case-control	222	1,356	Relation between BMI, alcohol, and cigarette smoking and EAC risk.	Structured questionnaire	Current cigarette smoking was a significant risk factor for EAC. Cigarette smoking had a long-lasting deleterious effect, even 20 years after smoking cessation. Alcohol use was not associated with an increased risk. There was also a statistically significant increase in EAC risk in a dose-dependent manner with increasing BMI measured at ages 20 and 40 years.

Abbreviations: AU, Australia; BEAGESS, Barrett's and Esophageal Adenocarcinoma Genetic Susceptibility Study; BMI, Body Mass Index; CA, Canada; CI, Confidence Interval; CN, China; CSDs, Carbonated Soft Drinks; CT, Computed Tomography; CZ, Czech Republic; DE, Germany; DII, Dietary Inflammation Index; EAC, Esophageal Adenocarcinoma; EPIC, European Prospective Investigation into Cancer and Nutrition; FFQ, Food Frequency Questionnaire; GERD, Gastroesophageal Reflux Disease; GI, Glycemic Index; GL, Glycemic Load; GPRD, General Practice Research Database; GR, Greece; HHHQ, Health Habits and History Questionnaire; IE, Ireland; LBS, Pounds; MetS, Metabolic Syndrome; Mg, Magnesium; NCL, National Cancer Institute; NL, Netherlands, OR, Odds Ratio; PL, Poland; RO, Romania; RU, Russia; RR, Relative Risk; SE, Sweden; UK, United Kingdom; US, United States, y, years.

Table 3 Characteristics of included cohort and cross-sectional studies, in alphabetical order

Author year [Ref]	**Study period** **Country**	**Study design**	**EAC cases (n)**	**Study population (n)**	**Aims**	**Data**	**Main results**
Abnet et al. 2008 [97]	1995-1996 (7y FU) US	Cohort (NIH-AARP Diet and Health Study)	371	480,475	Evaluating the association between BMI and risk of developing EAC.	Mailed questionnaire eliciting information on demographics, dietary intake and health-related behaviors.	For EAC, each of the 3 BMI categories greater than normal (<18.5; 18.5-25; 25-30; 30-35;>35) had significant and progressively greater risk.

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						Cancer data from the Cancer Registry databases.	
Allen et al. 2009 [98]	1996-2001 (7y FU) UK	Cohort (The Million Women Study)	226	1,280,296	Association between moderate alcohol intake and risk of EAC in women.	Questionnaire without any other details.	No statistically significant association was found between any threshold of alcohol intake (≤2; 3-6; 7-14; ≥15 drinks/week) and EAC.
Carman et al. 2009 [99]	1995-1996 (7y FU) US	Cohort (NIH-AARP Diet and Health Study)	382	492,559	Association of dietary α-tocopherol, γ-tocopherol, and supplemental vitamin E with the risk of EAC.	124-item FFQ	α-tocopherol: borderline significantly increased risk of EAC. Supplemental Vitamin E: no association with EAC; γ-tocopherol: no association with EAC risk.
Cook et al. 2013 [100]	1995-1996 (10y FU) US	Cohort (NIH-AARP Diet and Health Study)	631	303,033	To investigate the relationship between physical activity, sedentary behavior, and EAC.	Self-administered baseline questionnaire. Mailed risk factor questionnaire (after 6 months from baseline).	Inverse association between sedentary behavior and EAC.
Cross et al. 2011 [101]	1995-1996 (10y FU) US	Cohort (NIH-AARP Diet and Health Study)	630	494,979	To investigate the relationship between meat and meat-related variables and EAC.	Self-administered baseline questionnaire. 124-item FFQ. Mailed risk factor questionnaire (after 6 months from baseline).	Red meat, with meat and processed meat consumption, was not associated with EAC. A high HCA intake was associated with borderline statistically increased risk of EAC. Positive association between heme iron intake and EAC. No association between B[a]P, nitrate, or nitrite and EAC.

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Dawsey et al. 2014 [102]	1995-1996 (10y FU) US	Cohort (NIH-AARP Diet and Health Study)	625	490,593	To investigate the association between multivitamins and other supplements and EAC.	Self-administered baseline questionnaire.	Statistically significant association between multivitamin use in smokers and EAC. Inverse association between iron supplement use and EAC risk. Direct association between calcium supplement use and EAC risk.
de Jonge et al. 2007 [103]	2002-2005 NL	Cross-sectional	126	226	To investigate the relation between environmental risk factors and EAC.	Standard questionnaire	BMI and a smoking habit were related to a higher EAC risk in males.
Engeland et al. 2004 [104]	1963-2001 NO	Cohort	575	2,001,617	To investigate the association between BMI, stature, and cancer.	Height and weight measured by trained staff.	Being overweight and obese were strictly related to a higher risk of EAC.
Freedman et al. 2007 [105]	1995-1996 (5y FU) US	Prospective cohort (NIH–AARP Diet and Health Study)	205	474,606	To investigate the association between tobacco, alcohol, and the risk of EAC.	Self-administered validated questionnaires concerning alcohol intake and tobacco.	Current and former cigarette smoking was associated with increased risk of EAC. No association between drinking more than three alcoholic drinks per day and EAC.
Freedman et al. 2007 [106]	1995-1996 (5y FU) US	Cohort (NIH-AARP Diet and Health Study)	213	490,802	To investigate the association between fruit and vegetable consumption and the risk of EAC.	Self-administered baseline questionnaire 124-item FFQ	No association between total fruit and vegetable consumption and EAC risk. Spinach intake was significantly associated with reduced EAC risk.
Gatenby et al. 2008 [107]	1996-2004 UK	Hospital-based prospective cohort		1,651	To investigate the association between demographic characteristics, lifestyle, and EAC risk.	Information from patient hospital records.	No association between gender, smoking habits, alcohol consumption and the incidence of EAC.

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Gonzalez et al. 2006 [108]	1992-1998 DK, FR, DE, GR, IT, NL, NO, ES, SE, UK	EPIC - Cohort	65	481,518	To describe the effect of fruit and vegetable intake on the risk of EAC.	12-month previous country-specific validated FFQ. Most centers adopted a self-administered dietary questionnaire that included 88 – 266 food items. Food record (United Kingdom and Sweden). Lifestyle questionnaire.	Negative with a non-significant negative association for vegetable intake and citrus intake.
Gonzalez et al. 2006 [109]	1992 - 2002 DK, FR, DE, GR, IT, NL, ES, SE, UK	EPIC - Cohort	65	481,518	To investigate the risk of EAC associated with the consumption of meat and processed meat.	12-month previous country-specific validated FFQ. Most centers adopted a self-administered dietary questionnaire that included 88 – 266 food items. Food record (United Kingdom and Sweden). Lifestyle questionnaire.	Positive but no statistically significant association between EAC risk and total and processed meat intake in the calibrated model.
Hardikar et al. 2013 [110]	1995-2009	Prospective cohort	45	411	Association between smoking,	Structured personal 45-minute interview.	Increased risk of EAC was associated with smoking

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	US	(Seattle Barrett's Esophagus Study – SBES)			school, and obesity and EAC.	Anthropometric measurement (weight, height, waist, and hip circumferences).	duration and cumulative exposure. No association between alcohol consumption and EAC risk. No association between BMI and EAC risk. Modest increased risk of EAC in males with abdominal obesity.
Huerta et al. 2010 [111]	1991-2005 DK, FR, DE, GR, IT, NL, ES, SE, UK	Prospective cohort (EPIC)	80	420,449	To investigate the association between physical activity and EAC.	Validated questionnaires; CPAI.	Physical activity was not associated with EAC.
Jakszyn et al. 2013 [112]	FR, IT, ES, UK, NL, SE, DE, DK	Prospective cohort (EPIC)	137	481,419	To investigate the association between the intake of different types of meats, heme iron intake and EAC risk.	Validated center-specific questionnaires.	Heme iron intake and processed red meat were significantly associated with EAC, but not white and unprocessed meat (based on tertiles of intake). Moreover, any associations remained significant when the intake was considered as a continuous variable.
Ji et al. 2017 [113]	1973-2010 SE	Retrospective cohort	145	420,489	To investigate the association of alcohol consumption with EAC.	Swedish Hospital Discharge Register and Outpatient Register; Crime	Subjects with alcohol use disorders (heavy alcohol drinkers) had an increased risk of EAC.

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						Register; Prescription Drug Register.	
Keszei et al. 2012 [114]	1986-2002 NL	Case-cohort The Netherlands Cohort Study (NLCS)	145	3,921 (sub-cohort)	To investigate the association between red and processed meat and the risk of EAC.	Self-administered baseline questionnaire with a 150-item questionnaire on food and beverage consumption during the year prior to the start of the study.	No association between EAC risk and red meat and processed meat intake.
Keszei et al. 2013 [115]	1986-2002 NL	Case-cohort The Netherlands Cohort Study (NLCS)	151	4,032 (sub-cohort)	Relation between the risk of EAC and dietary intake of N-nitroso-dimethylamine, heme iron, nitrite, and nitrate.	Self-administered baseline questionnaire with a 150-item questionnaire on food and beverage consumption during the year prior to the start of the study.	No associations between N-nitroso compounds and EAC risk.
Levi et al. 2013 [116]	1967-2006 IL	Cohort	28	1,088,242	To investigate the association between BMI in late adolescence, SES and ethnic factors and EAC incidence.	Measured height and weight; Israeli Central Bureau of Statistics; Israel National Cancer Registry.	Risk of EAC was not significantly increased in subject with BMI ≥85th percentile. No association between SES, ethnicity, and EAC.

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Li et al. 2013 [117]	1995-2006 US	Cohort (NIH-AARP Diet and Health Study	633	494,968	To investigate the association between HEI-2005, aMED and the risk of EAC	124-food item FFQ; HEI-2005 aMED; Social Security Administration; Death Master File; Cancer registers.	Higher HEI-2005 was significantly associated with a reduced risk of EAC. No association between the aMED score and the risk of EAC.
Lin et al. 2015 [118]	1995-1997 2006-2008 NO	Cohort CONOR and HUNT3	62	192,903	To investigate the role of the metabolic syndrome and WC.	Anthropometric data measured objectively.	Metabolic syndrome was not associated with EAC, whilst a WC higher than 80 cm in women and 94 cm in men was significantly associated with an increased risk of EAC.
Merry et al. 2007 [119]	1986-1999 NL	Prospective cohort (The Netherlands Cohort Study on Diet and Cancer)	133	4,552 sub-cohort	To investigate the association between BMI and EAC risk.	Self-administered questionnaire on usual dietary intake, anthropometry, smoking habits, physical activity, education, and history of cancer.	Overweight and obesity (BMI ≥25 kg/m^2) were associated with EAC risk. Change in BMI during adulthood was positively associated with the risk of EAC. No association with BMI in early adulthood. No association between EAC risk and height.
O'Doherty et al. 2012 [120]	1995-2006 US	Cohort (NIH-AARP Diet and Health Study	630	494,978	To investigate the association between total fat and fat subtype intake and EAC.	Baseline questionnaire; 124-food item FFQ.	No consistent associations between total fat intake and fat subtypes with risk of EAC. Protective role of polyunsaturated fat intake was seen for EAC in subjects with a normal BMI.

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O'Doherty et al. 2012 [121]	1995-2006 US	Cohort (NIH-AARP Diet and Health Study	253	218,854	To investigate the relation between height, BMI, and abdominal obesity with EAC.	Baseline questionnaire; Risk factor questionnaire.	BMI≥35 *vs* BMI 18-25 was positively associated with EAC. WC was positively associated with EAC. WHR was positively associated with EAC.
Petrick et al. 2017 [122]	1995-1996 US	NIH-AARP Diet and Health Study and Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial	633	409,796	To assess the effects of adiposity over the life course and EAC.	Self-reported anthropometric data.	Being overweight in early adulthood and weight gain later in life were also associated with an increased risk of EAC.
Reeves et al. 2007 [123]	1996-2001 (5.4y FU) UK	Million Women Study	150	1,222,630	To examine the relation between BMI and EAC.	Self-reported anthropometric data.	Increasing BMI is associated with a significant increase in the risk of EAC.
Ren et al. 2010 [124]	1995-1996 (13y FU) US	NIH-AARP Diet and Health Study	305	566,407	To investigate the relation between hot beverages, tea, coffee, carbonated soft drinks, and EAC.	Baseline questionnaire; Risk factor questionnaire.	No significant association with hot beverages, tea, coffee, and carbonated soft drinks.
Samanic et al. 2006 [125]	1971-1999 SE	Cohort	82	362,552 males	To examine the relationship between being overweight, obesity, and EAC risk.	Measured weight and height. Population-based Swedish cancer registry.	Compared to men of normal weight, overweight and obese men had a significantly increased risk of EAC.

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Sanikini et al. 2020 [126]	10 European countries (DK, FR, DE, GR, IT, NO, ES, SE, NL, UK)	Cohort EPIC	220	476,16	To investigate anthropometric factors in relation to EAC.	Anthropometric measurements were taken at recruitment by trained health professionals.	WC and WHR were associated with a higher risk of EAC in both men and women.
Steevens et al. 2010 [127]	1986-2002 NL	Cohort (Netherlands Cohort Study on diet and cancer)	145	3,962 sub-cohort	To investigate the association between alcohol consumption, cigarette smoking, and the risk of EAC.	Self-administered questionnaire with a 150-item food FFQ.	No association between total alcohol and type of alcoholic beverage consumption and EAC risk. Frequency and pack-years of smoking were independently associated with risk of EAC. Risk reduction for smoking cessation and EAC was statistically significant.
Steevens et al. 2010 [128]	1986-2002 NL	Cohort (Netherlands Cohort Study on diet and cancer)	129	2,072 sub-cohort	To prospectively investigate the association between prediagnostic toenail selenium levels and risk of EAC.	Self-administered questionnaire with a 150-item FFQ and questions on cancer risk factors (smoking habits, alcohol consumption, height, and weight). Toenail clippings for selenium determination by neutron activation analysis of the 77mSe isotope.	Inverse association between selenium status and risk of EAC in subgroups (women; never smokers; low antioxidant consumers).

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Steevens et al. 2011 [129]	1986-2002 NL	Cohort (Netherlands Cohort Study on diet and cancer)	144	4,035 sub-cohort	To prospectively investigate the role of vegetable and fruit consumption in the development of EAC.	National Cancer Registry Nationwide Network; Registry of Histopathology and Cytopathology in the Netherlands; Self-administered questionnaire with a 150-item food FFQ.	Significant inverse associations were observed for raw vegetables and EAC risk. No clear association between EAC risk and the consumption of legumes, pulses, allium vegetables, and cooked leafy vegetables. Inverse association between raw leafy vegetables and EAC. Moderate risk reduction associated with Brassica vegetable consumption. Citrus fruits were inversely associated with EAC. Total fruit consumption was associated with a non-significant decrease in EAC risk. Total vegetable consumption was only inversely associated with EAC risk in women. In current smokers only, vegetables were inversely associated with EAC risk.
Steffen et al. 2009 [130]	1992-2007 DK, DE, IT, NL, ES, SE, UK	EPIC - Cohort	124	391,456 Sub-cohort	To evaluate the relation between body height and general and abdominal obesity, with the incidence of EAC.	Directly measured weight, height, waist circumference, and hip circumference; non-dietary questionnaires for lifestyle and health-related information; country-specific FFQ.	BMI, high WC, and high WHR were statistically positively related to the risk of EAC. Body height was not associated with the risk of EAC. On a continuous scale, a 1 kg/m^2 higher BMI, a 5 cm higher WC, or a 0.1 unit higher WHR were related to a 1.08-fold and 1.16-fold or 1.59-fold higher risk of EAC, respectively. BMI and WC may be strongly associated

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							with the risk of EAC in smokers, rather than in non-smokers.
Steffen et al. 2015 [131]	1993-2008 DK, DE, IT, NL, ES, SE, UK	EPIC - Cohort	88	346,544 sub-cohort	Association of anthropometric measures with risk of EAC.	Directly measured weight, height, waist circumference, and hip circumference; Lifestyle questionnaires for lifestyle and health-related information; country-specific FFQ.	BMI was unrelated to EAC. WC showed a strong positive association with EAC risk. Hip circumference (HC) was inversely related to EAC after controlling for WC Protective effect of gluteofemoral (subcutaneous) adipose tissue in EAC.
Vermeulen et al. 2013 [132]	1992-2010 DK, FR, DE, GR, IT, NO, NL, ES, SE, UK	EPIC - Cohort	142	477,312	To investigate the association between dietary flavonoid intake and EAC risk.	Validated dietary country-specific questionnaires.	No statistically significant association between any flavonoid subclass and EAC.
Xiao et al. 2014 [134]	1995-2006 US	Cohort (NIH-AARP Diet and Health Study)	574	492,292	To investigate the association between folate, methionine, vitamin B6, and vitamin B12 intake and EAC risk.	Self-administered 124-item FFQ.	Higher intakes of folate, methionine, vitamin B6, or vitamin B12 were not associated with EAC risk. No association between total folate (diet+supplements) intake and EAC risk.
Yates et al. 2014 [133]	1993-2008 UK	EPIC-Norfolk Cohort	66	24,068	To investigate the relation between smoking,	EPIC questionnaire.	BMI greater than 23 kg/m^2 was associated with an increased risk of EAC. Statistically significant increased

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					BMI, alcohol consumption and EAC risk.		risk in subjects with a BMI >35. Inverse association with ≥7 units alcohol/week from wine.
Zamora-Ros et al. 2014 [135]	1992-2010 DK, FR, DE, GR, IT, NL, ES, SE, UK	EPIC - Cohort	339	442,143	To investigate the relationship between tea (mainly black tea) and coffee (total, caffeinated and decaffeinated) intake and EAC risk.	Validated dietary country-specific questionnaires; personal interview (GR, ES, Ragusa); short non-quantitative FFQ + 7-day dietary diary (SE); questionnaire on sociodemographic characteristics; questionnaire on physical activity and leisure time; directly measured weight and height (except in UK and FR); information on coffee and tea consumption (only in DE, NL, and UK)	No statistically significant association between the intake of tea, mainly black tea, and coffee and EAC risk.
Zendehdel et al. 2008 [136]	1971-2004 SE	Retrospective cohort	130	336,381	To investigate the relation between smokers and users of Scandinavian moist	200-item questionnaire	The use of snus was not statistically significant for EAC risk. Compared to never-users of any tobacco,

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	snuff and EAC risk.	smokers had increased risks of EAC.

Abbreviations: aMED, Alternate Mediterranean Diet; AU, Australia; B[a]P, Benzo[a]pyrene; BEAGESS, Barrett's and Esophageal Adenocarcinoma Genetic Susceptibility Study; BMI, Body Mass Index; EAC, Esophageal Adenocarcinoma; CPAI, Cambridge Physical Activity Index; CA, Canada; CI, Confidence Interval; CN, China; CSDs, Carbonated Soft Drinks; CT, Computed Tomography; CZ, Czech Republic; CONOR: Cohort of Norway; DE, Germany; DII, Dietary Inflammation Index; EAC, Esophageal Adenocarcinoma; EPIC, European Prospective Investigation into Cancer and Nutrition; FFQ, Food Frequency Questionnaire; FU, follow-up; GERD, Gastroesophageal Reflux Disease; GI, Glycemic Index; GL, Glycemic Load; GPRD, General Practice Research Database; GR, Greece; HCAs, Heterocyclic amines; HHHQ, Health Habits and History Questionnaire; HEI-2005, Healthy Eating Index-2005; HUNT3: third Nord-Trøndelag Health Study; IE, Ireland; LBS, Pounds; MetS, Metabolic Syndrome; Mg, Magnesium; NCL, National Cancer Institute; NL, Netherlands, OR, Odds Ratio; PL, Poland; RO, Romania; RU, Russia; RR, Relative Risk; SE, Sweden; SES, Socioeconomic Status; UK, United Kingdom; US, United States; WC, Waist circumference; WHR, Waist-to-hip ratio, y, years.

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3.2 Anthropometric measures

'Keep your weight within the healthy range and avoid weight gain in adult life' is the first recommendation given by the WCRF/AICR in 2018 [10]. A healthy weight range means a normal range of body mass index (BMI). BMI is defined by the World Health Organization (WHO) as the weight in kilograms divided by the square of the height in meters (kg/m^2) [137]. Subjects are in a normal weight range when BMI falls within the range of 18.5-24.9, whereas they are defined as overweight if their BMI is 25.0-29.9, and obese if this is ≥30.0. With regard to weight control, several case-control and cross-sectional studies have demonstrated the association between a high BMI and the risk of EAC [75, 88, 36, 38-40, 42, 63, 65, 81, 95, 45, 103, 32, 53, 57]. The studies included in our systematic review found a statistically significant higher risk of EAC in obese patients. The risk increased by fourfold on average in the heaviest quartile compared with the lightest quartile of BMI. Excess weight is a strong risk factor for EAC, with risk rising consistently as BMI increases. Risk appeared to be largely related to elevated BMI *per se* and not to weight gain or loss during adult life [39]. Furthermore, by comparing subjects in the lowest 10% of normal BMI (<21.70 Kg/m^2 for men and <20.18 Kg/m^2 for women) with those in the highest decile (≥ 29.54 Kg/m^2 for men and ≥31.25 Kg/m^2 for women), the risk of EAC increased steadily to reach fivefold (OR = 5.4, 95% CI = 2.4–12.0) [39]. The association between BMI and EAC does not seem to be affected by symptomatic gastroesophageal reflux, although it appears to be synergic with BMI [40, 63, 81, 75, 57]. Visceral adipose tissue is another risk factor in the development of EAC and seems to be more important than obesity *per se* [65]. A larger abdominal diameter (with and without adjustment for BMI) was a risk factor for EAC, with a 10% increase in EAC risk for every centimeter of increased abdominal diameter in subjects with an abdominal diameter (anterior-posterior diameter) of >20cm [40]. Furthermore, in women, BMI at around 20 years of age was positively associated with EAC risk. Drahos et al.[43] and Lin et al.[118] also investigated the relationship between other conditions often associated with obesity, such as metabolic syndrome (MetS), hypertension, hypercholesterolemia, and diabetes and the risk of EAC. In their study, the authors reported that obesity and hypertension were associated with EAC, but high cholesterol, type 2 diabetes, and MetS were not. All the cohort studies analyzed also confirmed previous case-control study results [97, 119, 121, 125, 122, 104, 130, 133, 123], apart from those of Levi et al. who failed to find a statistically significant association [116]. For EAC, each of the three BMI categories greater than normal (BMI 25- <30 Kg/m^2; 30 - <35 Kg/m^2; ≥35 Kg/m^2) significantly and progressively increased the risk of cancer. Literature results confirm that BMI at baseline is a strong risk factor for EAC, and a change in BMI during adulthood increased the risk [119]. Being overweight in early adulthood and weight gain later in life were also associated with an increased risk of EAC [122]. Moreover, waist circumference [121, 126, 118, 131, 130], abdominal obesity [110], hip circumference, and waist-hip ratio (WHR) [121, 126] were associated with a higher risk of EAC. In particular, on analyzing data from the European Prospective Investigation into Cancer and Nutrition (EPIC) study, Steffen et al.[131] reported that abdominal, rather than general obesity, is a strong and robust risk factor for EAC. The authors also provide new evidence on the protective effect of gluteofemoral (subcutaneous) adipose tissue in EAC. These results were also obtained in a two-stage control function instrumental variable method of the Mendelian randomization analysis aimed at estimating the unbiased and unconfounded effect of BMI on the risk of EAC [86].

3.3 Physical activity

'Be physically active as part of everyday life - walk more and sit less' is the second recommendation for cancer prevention proposed by the WCRF/AICR in 2018 [10]. Physical activity should be part of daily life. Indeed, the WCRF/AICR recommends at least 30 minutes of moderate-intensity activity per day, which can include occupational, transport, household, or leisure activities [9]. However, physical activity of a longer duration or greater intensity shows more beneficial health outcomes. Few studies investigating the association between physical activity and EAC are available. Data from the EPIC cohort

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show no association between EAC and any kind of physical activity (occupational, recreational, and household) at any level of intensity [111]. In 2013, Cook et al. [100] also reported no association between physical activity and EAC risk. The authors surprisingly showed an inverse association between sedentary behavior and EAC risk. In the multivariable Cox proportional hazards regression analysis, this inverse association was statistically significant ($p<0.05$) in subjects who watched TV for 3-4 hours/day (HR=0.55, 95% CI 0.36, 0.84) and 5-6 hours/day (HR=0.57, 95% CI 0.36, 0.92). However, these results were not statistically significant after adjusting for multiple testing. A statistically significant association was instead found by Vigen et al. [89]. Indeed, in their population-based case-control study, a decreased risk of EAC was associated with an increase in the Total Activity Index (OR = 0.67, 95% CI = 0.38, 1.19) for the highest versus lowest quintile.

3.4 Dietary patterns, food groups, and beverages

The WCRF/AICR report suggests "Limit consumption of 'fast foods' and other processed foods high in fat, starches, or sugars" [10]. In this section, we analyzed the literature concerning the association between dietary patterns and EAC. In particular, we retrieved thirteen studies (twelve case-control studies [33, 36, 50, 66, 70, 64, 71, 94, 56, 74, 96, 87], and one cohort study [117]) examining the relationship between dietary patterns and EAC. In their 2001 US multicenter case-control study, Mayne et al. [66] reported an association between dietary patterns in which the majority of nutrients are consumed primarily from plant-based foods (dietary fiber, carbohydrates, polyunsaturated fat, and vegetable protein) and a reduction of EAC risk. Conversely, a higher intake of nutrients primarily provided by foods of animal origin (saturated fat, animal protein, and cholesterol) is associated with an increased risk. Chen et al. [36] considered six dietary patterns in their analysis: "healthy food", "high in meat", "high in salty snacks", "high in desserts", "high in milk", and "high in white bread". The analysis of EAC risk derived from individual dietary patterns showed a 3.6-fold higher risk of EAC for the "high in meat" pattern, a 2.9-fold higher risk for the "high in salty snacks" pattern, and a 2.6-fold higher risk for a diet "high in white bread". In contrast, the daily consumption of fish, all vegetables, citrus fruit and juices, and dark bread were each associated with a 50% lower EAC risk. In one study, the authors classified patients into three dietary patterns [33]: (i) a "healthy diet" (prevalence of vegetables, tomatoes, fruit, fish, and poultry); (ii) a "western diet" (prevalence of processed meat, red meat, sweets, high-fat dairy, and high-fat gravy); (iii) "alcohol drinker" (including French fries and alcoholic beverages such as beer and liquor). In this study, they found that the healthy diet pattern was, in general, associated with a moderately, non-statistically significant reduced risk. In contrast, the western diet pattern was associated with a modestly increased risk of EAC (highest v. lowest tertiles, OR= 1.6, 95% CI 0.9-3.1, p for trend = 0.130). Navarro Silvera et al. [70] reported a significantly increased risk of EAC in subjects with a dietary pattern characterized by a high intake of meat (particularly red meat), and a low intake of vegetables and fruit. In particular, when analyzing food subgroups they found that red meat, high-fat dairy, and refined grains were associated with an increased risk of EAC with an estimated OR=3.02, (95% CI 1.65-5.52); 1.36, (95% CI 1.10-1.67); 1.27 (95% CI 1.02-1.59), respectively, whereas raw vegetables were associated with a decreased risk with an estimated OR of 0.79 (95% CI 0.63-1.00). The same author confirmed these results in 2011, performing pattern analyses of dietary and lifestyle factors in relation to EAC risk [71]. Particularly for the "fruit/vegetable" pattern, (mainly composed of deep yellow/orange and dark green and cruciferous vegetables, tomato products, citrus and non-citrus fruit) and the "meat/nitrite" pattern (mainly composed of nitrite, high-nitrite meats, and red meats). Significant inverse associations with the risk of EAC were found in the highest quartile of intake in the "fruit/vegetable pattern" when compared with the lowest quartile (OR Q4 *v.* Q1= 0.43, 95% CI 0.26-0.71; p for trend <0.001). However, results regarding the "meat/nitrite" pattern were contrariwise. The authors reported a significant positive association for this pattern between EAC risk and the highest quartile of intake compared with the lowest (OR Q4 *v.* Q1 = 5.61, 95% CI 2.81, 11.20; p for trend <0.001). Ibiebele et al. [50] used three dietary patterns in their analysis:

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(i) “meat and fat”; (ii) “pasta and pizza”; (iii) “fruit and vegetables”. The authors found no association between EAC risk and the “pasta and pizza” and “fruit and vegetable” patterns. A statistically significant association was found between EAC risk and the “meat and fat” dietary pattern, characterized by a high intake of processed meat, high-fat potato, discretionary fat, red meat, high-fat dairy, poultry with skin on, white bread, sweet snacks and fatty spreads, and a very low intake of fruits, vegetables, and fish. An increased risk of EAC [OR 2.12 (95% CI 1.30- 3.46)] was shown for this dietary pattern. After an analysis of the individual food that strongly contributes to the pattern, this association seems to be driven in part by high-fat dairy foods that have an OR of 2.46 (95% CI 1.54-3.94). In a large cohort study with almost 500,000 participants (women and men), Li et al. [117] examined the association of 2 diet quality indexes: the Healthy Eating Index-2005 (HEI-2005) (measure of diet quality as specified by the Federal dietary guidance and the publication of the Dietary Guidelines for Americans 2005) [138] and the Alternate Mediterranean Diet (aMED) scores [139] (which include total vegetables, excluding potatoes, total fruit, nuts, legumes, fish, whole grains, monounsaturated fats/Saturated Fatty Acid ratio, alcohol, and red and processed meat) and the risks of EAC. Higher HEI-2005 scores were associated with a significantly-reduced risk of EAC. With regard to the aMED, the authors did not observe a significant association with EAC risk. For individual foods, total grains within HEI-2005 and legumes within aMED were inversely related to EAC risk. A recent study focusing on the relationship between the dietary inflammatory index (DII) [140] and the risk of EAC was performed by Lu et al. [64]. A higher dietary inflammatory index score indicates a more pro-inflammatory diet. An analysis of completed food frequency questionnaires (FFQ) by participants showed positive, statistically significant associations between DII scores and the risk of EAC (OR 3.59, 95% CI 1.87-6.89). The study suggests that diet-related inflammation may contribute to the etiology of EAC. A dietary pattern with a high proportion of carbohydrates showed a decreased risk of EAC [56, 94], while a high proportion of fat increased the risk [56, 74, 96, 87]. In detail, O'Doherty et al. [74] reported an increased risk of EAC in subjects with a high intake (53.8-54.8 g/day) of saturated fat (OR = 2.41; 95% CI 1.14–5.08; p for trend = 0.010), monounsaturated fat (41.2-41.4 g/day) (OR = 5.35; 95% CI 2.14–13.34; p for trend <0.01), polyunsaturated fat (24.8 and 27.7 g/day) (OR = 2.68; 95% CI 1.23–5.85) and cholesterol (462.3-484.7 g/day) (OR = 3.59; 95% CI 1.71–7.54; p for trend <0.01). Opposite results on fats were obtained from a very large US cohort study involving almost 500,000 men and women [120]. Following a multivariate analysis, this study found no association between total fat/fat subtypes and EAC risk. The authors only demonstrated a non-significant possible protective role of polyunsaturated fat against EAC. Total protein in the diet does not seem to influence the risk of EAC [56] although Wolfgarten et al. [94] reported an increased risk associated with the intake of animal proteins ≥75g day OR of 2.3 (95% CI 0.70-6.80).

3.4.1 Foods of plant origin and dietary fiber

‘Eat a diet rich in wholegrains, vegetables, fruit, and beans’. Fruit and vegetables, as well as legumes and whole grains, are the main sources of dietary fiber. According to the WCRF/AICR, fiber intake is likely to protect against several cancers [10]. To our knowledge, the first study evaluating the association between vegetable/fruit consumption and EAC risk was Tzonou et al. in 1996 [87]. In this study, the consumption of vegetables and fruit, as well as the intake of crude fiber, were inversely associated with EAC [87]. A high intake of fruit and vegetables (≥4 servings/day) showed a strong protective effect. Individuals eating ≥4 servings/day of fruit and vegetables had a 50-75% lower risk of EAC; however, no significant associations were found between any specific fruit or vegetable and EAC [84, 80]. In 2007, Freedman et al. [106] found a significant association between Chenopodiaceae (Spinach) intake and a low risk of EAC [Q3 v. Q1, HR 0.66 (95% CI 0.46-0.95)] and a suggestive but not significant association between cruciferae (broccoli, cauliflower, brussels sprouts, turnip, cabbage, coleslaw, collard greens, mustard, and kale), graminacae (corn), leguminosae (dried beans, string beans, and peas) and EAC risk reduction. Results from Freedman et al. were confirmed by Steevens et al. [129] who

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showed a significant inverse association between raw leafy vegetable intake and EAC risk [Relative Risk (RR) per 25 g/day: 0.81 (95% CI 0.68–0.98)], while the consumption of Brassica vegetables was associated with a slightly decreased risk of EAC per 25 g/day increments [RR 0.85 (95% CI 0.49-1.48)], as were tomatoes [RR 0.79 (95% CI 0.61-1.01)] and onions [RR 0.84 (95% CI 0.65-1.09)]. In the EPIC study, the authors also showed a negative, although non-significant, association between vegetable intake (calibrated HRs 0.72; 95% CI 0.32–1.64 per 100g of increase) and EAC risk. They also found a borderline non-significant negative association of leafy vegetable intake (p for trend 0.070) for EAC [108]. A possible protective role of fruit in reducing EAC risk was confirmed in several studies. Cheng et al. [38] showed the strong protective effect of high fruit consumption in women with a clear linear trend (p = 0.003) from the lowest to the highest level of intake. Also, Anderson et al. [32] showed a protective role of fruit [OR=0.50 (95% CI 0.30-0.86)], while Gonzalez et al. [108], Freedman et al. [106], and Steevens et al. [129] demonstrated a non-significant negative association between fruit intake and EAC risk; however, Steevens et al. [129] reported an inverse association of citrus fruits with EAC [RRs for highest *v*. lowest intake: 0.55 (95% CI 0.31–0.98)]. In their case-control study, Wu et al. (2007) found that fiber intake had a protective effect against EAC [96]. The study conducted in California involved 206 cases of EAC and 1,308 control subjects. The validated 124-item FFQ was administered by means of an interview and referenced data pertaining to one year prior to diagnosis. A high total fiber intake (>15 g/day) was associated with a statistically significant reduction of EAC risk (OR=0.44, 95% CI0.3-0.8 p=0.004) and this inverse association appeared to have a stronger effect if the fiber source originates from fruit (p= 0.004) and vegetables (p< 0.001) instead of cereals. Data confirming the strong association between fiber intake and EAC risk reduction were reported by Lahmann et al. [58]. Authors analyzing data from a large Australian population-based case-control study showed a statistically significant inverse association (p≤0.001) between fiber intake and the risk of EAC, with a risk reduction of 28-37% per 10 g/day.

3.4.2 Animal Products

With regard to animal products, the WCRF/AICR suggested 'Limit consumption of red and processed meat'[10]. However, results on the association between meat consumption and EAC risk are not unanimous. Ward et al. [90] found a significantly higher risk with increasing red meat intake (primarily processed meats and beef). In this case-control study, a high intake of processed meats was associated with an elevated risk of EAC, whereas a high beef intake was not. The highest frequency of intake of red meat (>8 times/week) and gravy (> 4 times/week) was associated with about a 2-fold increased risk (OR=2.0, 95% CI 1.0–4.0; OR= 2.3, 95% CI 1.0-5.0). Through the EPIC study, Gonzalez et al. [109] found a non–statistically significant association between EAC risk and total meat and processed meat intake, and a positive association between poultry intake and EAC. In another EPIC cohort study, Jakszyn et al. found a significant association between a higher intake of processed red meat and an increased risk of EAC (HR 2.27, 95% CI 1.33–3.89) when the third tertile of intake was compared with the lowest. However, the association did not remain significant when intake was considered as a continuous variable [112]. Lastly, in this study, no significant association was found between a higher intake of white meat or unprocessed meat and the risk of EAC [112]. Wu et al. (2007) found no association in their case-control study between total meat consumption and EAC risk [96]. However, the risk tended to increase for red and processed meat, but it was not statistically significant. In the Netherlands Cohort Study (NLCS) involving 120,852 subjects (58,279 men and 62,573 women), red and processed meat intake were not associated with EAC risk [114]. Another study showed no consistent association between total red meat (fresh and processed) intake and EAC risk, but patients in the highest level of intake (69.8-72.8 g/day) of fresh red meat had a higher risk of EAC compared to the controls (OR 3.15, 95% CI 1.38–7.20; p for trend= 0.010) [74]. An increase in EAC risk was seen in patients in the fourth quartile of corned beef/luncheon meat (OR 2.81, 95% CI 1.10–7.15) and in the fourth quartiles of beef and lamb intake (OR 2.53, 95% CI 1.03–6.19 and OR 4.61, 95% CI

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1.94–10.96, respectively). Those in the second quartile for sausage were also at increased risk of EAC (OR 3.28, 95% CI 1.50–7.18). In accordance with the majority of studies mentioned above, Navarro et al. reported in 2014 that consuming more than half a serving of red meat per day was associated with a high risk of EAC [72]. Moreover, the risk increased among people who consumed less than two servings of non-citrus fruit. As regards the consumption of dairy products, this showed a positive association with EAC risk (OR 1.89, 95% CI 1.02-3.50; p for trend=0.040), although it was not statistically significant [68].

3.4.3 Consumption of non-alcoholic beverages

The WCRF/AICR report suggests 'Limit consumption of sugar sweetened drinks' [10]. According to a case-control study, the intake of sweetened beverages was associated with an increased risk of EAC [59]. To the contrary, two case-control studies show no association between carbonated soft drink consumption and risk of EAC. In particular, Lagergren et al. conducted a study among a Swedish population [55]. The study enrolled 189 patients and 820 controls. They conducted an interview to investigate the food and beverage consumed 20 years earlier. Mayne et al. [67] conducted another case-control study in 2006 having a similar study design and sample size (282 cases and 687 controls). They conducted a survey evaluating the beverages consumed 5 years earlier and they found an inverse association between carbonated soft drink consumption and the risk of EAC.

Contrasting results also emerged for hot beverages (>65 °C), tea, and coffee consumption, as confirmed by limited non-conclusive evidence reported by the WCRF/AICR [10]. In particular, we found two cohort [124, 135] and one case-control studies [48]. The case-control study [48] found a statistically significant association between hot or very hot beverages and EAC, whereas coffee consumption showed a dose-response increased risk that was not statistically significant. Similar results were also found in the two cohort studies [124, 135], particularly the most recent EPIC cohort study [135] which evaluated the possible relationship between coffee and tea consumption and the risk of EAC. They found no statistically significant association between tea and coffee consumption and esophageal cancer even after exploring the two histological types (EAC and squamous). The dose-response increased risk was confirmed for coffee consumption, even if not significant, while an inverse but not significant association between tea consumption (in particular black tea) and EAC was found. There was also no statistically significant interaction between tea/coffee intake and baseline alcohol intake or BMI.

3.5 Vitamins, minerals, and other nutrients

The WCRF/AICR report suggests 'Do not use supplements for cancer prevention. Aim to meet nutritional needs through diet alone' [10]. A recent large US population-based study reported a risk reduction of around 57% (OR 0.43, 95% CI 0.29-0.66) for EAC incidence due to dietary anthocyanidins, although a modest 13% decreased risk of mortality among EAC patients was observed [79]. A non-statistically significant association between a dietary intake of flavonoids and overall EAC risk was reported in the EPIC cohort. Nevertheless, a significant inverse association between total dietary flavonoids (HR=0.84, 95% CI 0.71-0.99), flavonols (HR=0.86, 95% CI 0.74-0.99), flavanols (HR=0.72, 95% CI 0.56-0.92), and Flavan-3-ol monomers (HR=0.89, 95% CI 0.80-0.99) and EAC risk was only shown in current smokers [132]. Two Swedish nationwide and population-based case–control studies explored the association between a dietary intake of lignans, quercetin, and resveratrol and EAC risk. In the first study, the authors investigated the role of lignans on EAC risk, reporting a dose-dependent association between lignan intake and EAC, with a 35% reduced risk (OR= 0.65, 95% CI 0.38–1.12) in subjects with the highest lignan-rich food intake (wholemeal bread, vegetables, and fruits) compared with the lowest [62]. These results were confirmed more recently and the authors showed a strong association between the intake of lignans and other compounds, such as quercetin and resveratrol, and a decreased risk of EAC (OR 0.24, 95% CI 0.12-0.49) [61].

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3.5.1 Vitamin C

As regards vitamin C, the WCRF/AICR report [10] found limited non-conclusive evidence. However, we retrieved five case-control studies [34, 66, 69, 87, 83] which all reported the protective role of a dietary intake of vitamin C. The first findings by Tzonou et al. [87] in 1996 emerged from a hospital-based case-control study that showed an inverse association between vitamin C and EAC (OR 0.54 [95% CI 0.40-0.72]. These results were confirmed in nationwide population-based case-control studies from Sweden [83] and Germany [34]. Consistently, a multicenter case-control study [66], which particularly focused on vitamin C plant food, and an all-Ireland population-based case-control study [69] reported that patients with a lower risk of EAC are those with the highest intake of vitamin C. In particular, the latter found a significant reduction (OR 0.37, 95% CI 0.21–0.66; p for trend = 0.001) for a vitamin C intake higher than 168 mg/day. A further reduction in risk in current smokers was found with the highest intake of vitamin C (OR 0.23, 95% CI 0.07–0.76).

3.5.2 Vitamin E

The WCRF/AICR report [10] found limited non-conclusive evidence on vitamin E. In our review, the association between Vitamin E and EAC risk was investigated in four case-control studies [51, 69, 83, 34] and one cohort study [99]. A significant risk reduction in the occurrence of esophageal tumor with an increased intake of vitamin E was reported by Bollshweiler et al. [34] and confirmed by Ibiebele et al. [51] in 2013. In particular, Ibebele et al. described a statistically significant decreased risk of EAC with a high intake (median daily intake 9.6 mg) of vitamin E from food sources (OR Q4 *v.* Q1 = 0.43, 95% CI 0.28–0.67) and from a combination of food and supplements (OR Q4 *v.* Q1=0.64, 95% CI 0.43–0.96). In contrast with these findings, two case-control studies [69, 83] and one large US prospective cohort study [99] involving 492,559 participants reported no association between Vitamin E, α-tocopherol, and γ-tocopherol intake and EAC risk.

3.5.3 Vitamin A and Carotenoids

The WCRF/AICR report [10] found limited non-conclusive evidence with regard to vitamin A and carotenoids. In our review, the association between EAC and the intake of vitamin A and carotenoid (total carotenoids, β-carotene, and β-cryptoxanthin) showed an inverse association in four [66, 35, 87, 83] of the five [66, 69, 35, 87, 83] studies analyzed. The majority of the studies reported a 40-50% risk reduction with evidence of dose-response at high intake. In contrast with previous results, Murphy et al. [69] reported in 2010 that an all-Ireland population-based case-control study resulted in no association between total carotenoid intake and EAC risk.

3.5.4 B Vitamins

The WCRF/AICR report [10] found limited non-conclusive evidence for B vitamins and specifically, pyridoxine (B6), folate, thiamin (B1), and riboflavin (B2). We found four studies (3 case-control and one cohort) that investigated folate intake and EAC risk [66, 134, 35, 82]. The three case-control studies reported an inverse significant association between folate intake and EAC, with an approximate 50% risk reduction as a result of high folate consumption [66, 35, 82]. Although previous studies found a significant inverse association between dietary folate intake and EAC, recent data from a large US cohort of 492,292 persons showed that higher folate intake is not associated with EAC risk. Moreover, no association was observed between total folate intake (diet + supplement) and EAC risk (p=0.150) [134]. Vitamin B6 showed an inverse association with EAC risk in one [66] out of two studies [66, 134] (OR 0.53, 95% CI 0.38-0.73). Opposite results were found for vitamin B12 [82], which shows a significant positive association with the risk of EAC (OR 1.39, 95% CI 1.10-1.76). In contrast with these results, in a recent large US cohort including almost 500,000 persons, Xiao, et al. [134] reported no association between the intake of vitamins B6 and B12 and EAC risk.

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3.5.5 Vitamin D and calcium

The association between EAC, vitamin D, and calcium are currently understudied. Indeed, specifically for calcium, the WCRF/AICR report [10] found limited non-conclusive evidence. An all-Ireland population-based case–control study evaluated the role of vitamin D and calcium in EAC risk [68]. The authors observed a significant direct association between subjects with the highest vitamin D intake (≥ 3.0-9.7 μg/day) compared with those at the lowest level of intake (< 2.05 μg/day). They reported an OR of 1.99 (95% CI 1.03-3.86; p for trend=0.020) even after adjustment for confounders. Dietary calcium does not seem to be associated with EAC risk [68].

3.5.6 Iron

In respect of the role of iron in EAC, the WCRF/AICR report [10] found limited non-conclusive evidence. In 2001, Wolfgarten, et al. [94] reported that a daily consumption of more than 18 mg of total iron (heme and non-heme iron) was inversely correlated with EAC, (OR 0.2, 95% CI 0.00-0.70). Moreover, two population-based case-control studies conducted in Ireland and in the US showed a positive direct association between heme iron intake and EAC risk [73]·[92]. The examined population in Ireland showed a significantly increased risk (OR 3.11, 95% CI 1.46-6.61) in subjects with a high level of heme iron intake (≥ 1.39 mg/d) and direct association per 1 mg/day increment (OR 1.91, 95% CI 1.18-3.09; p for trend=0.010) [73]. The same results were found in a population-based case control study conducted in Nebraska in which EAC was positively associated with higher intakes of heme iron (≥ 1440μg/day) OR 3.04, 95% CI 1.20–7.72; p for trend=0.009) and total iron from meat sources (≥ 5309 μg/day) (OR 2.67, 95% CI 0.99–7.16; p for trend=0.050) [92]. Consistent results were also found in the EPIC cohort study, according to which a higher intake of heme iron was significantly associated with a higher hazard of EAC (HR 1.67, 95% CI 1.05–2.68) [112]. Suggestive positive association was also found in a US cohort study [101] whereas, in a Netherland cohort study [115], researchers found no apparent associations between heme iron intake and EAC. On the other hand, non-heme iron intake showed a statistically inverse association (p for trend = 0.004) with EAC. This inverse association was confirmed per 10 mg/day increments (OR 0.29, 95% CI 0.08-0.99) [73]. However, contrary to the results from Ward et al. [91], three studies reported no association between EAC and nitrate, nitrite[101, 92, 115] and N-Nitroso Compounds (NOC), whose endogenous formation in the lower gastrointestinal tract in humans is also influenced by heme iron [115].

3.5.7 Other compounds

No significant association was observed for higher intakes of methionine (OR 0.85, 95% CI 0.66-1.10) [134]. The intake of magnesium (Mg) and EAC risk is controversial. In a German case-control study, the authors reported an inverse correlation between a daily Mg intake of more than 500 mg and EAC risk (OR= 0.20, 95% CI 0.07-0.42) [94]. A recent all-Ireland population case-control study [41] with 226 EAC cases showed no significant association between Mg intake and EAC risk (OR=0.77, 95% CI 0.30-1.99). In 2002, Chen, et al. [35] described an inverse association with a risk of EAC for dietary intakes of Zinc (OR=0.50, p=0.050), whereas no association between EAC risk and the intake of selenium, copper and zinc was found in a further study (P for trend =0.550; p for trend =0.790; p for trend=0.330, respectively) [69]. Conversely, an inverse association between selenium status and risk of EAC was shown in women, never smokers, and in low antioxidant consumers [128].

3.5.8 Dietary supplements

Concerning micronutrient intake from fortified foods and supplements and the relationship with EAC risk, Bollschweiler et al. [54] showed a significant risk reduction for EAC with increased folic acid intake. No associations were found between higher doses of a vitamin E supplement and the risk of EAC [99]. A recent large US cohort study with almost 500,000 subjects showed no significant association between multivitamin use and

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EAC risk [102]. As for an individual vitamin or mineral supplement intake, the authors found an inverse association between iron supplement use and the risk of EAC (HR=0.68, 95% CI 0.49- 0.94). A direct association emerged between EAC risk and the use of a calcium supplement (HR=1.27, 95% CI 1.06-1.52). No further associations were found with the intake of any other individual vitamin or mineral supplement (Zinc, Selenium, Folic Acid, Vitamin A, β-carotene, Vitamin C, Vitamin E) and EAC risk [102]. A protective role of vitamin C and multivitamin supplements was reported in only one study (OR 0.21, 95% CI 0.60-0.77) [87]. In a large population-based case-control study conducted in Ireland in 2010, the overall antioxidant index obtained by the combined intake of vitamin C, vitamin E, total carotenoids, and selenium was associated with a reduced risk of EAC (OR = 0.57; 95% CI =0.33–0.98) [69]. These findings were confirmed in 2013 through an Australian population-based case-control study, which demonstrated a decreased risk of EAC in subjects with a high score on the antioxidant index from food sources [51].

3.6 Cooking process and chemical modification during cooking

In 2007, the WCRF/AICR's guidance regarding "Preservation, processing, preparation: limit consumption of salt. Avoid mouldy cereals (grains) or pulses (legumes)" was included as one of the ten cancer prevention recommendations [9]. Although this recommendation was not mentioned as one of the ten final recommendations in the last edition of the WCRF/AICR expert report [10], the importance of preserving, processing and preparing food is mentioned in the report. We did not retrieve articles specifically analyzing salt consumption or exposure to aflatoxins and EAC, yet this recommendation is also in accordance with the "Continuous Update Project: Diet, Nutrition, Physical Activity, and Oesophageal Cancer" [10]. This paragraph presents results concerning modifications due to food preparation techniques and cooking processes. In the first population-based case-control study, frying, broiling, and grilling were the most commonly reported cooking techniques for beef [90]. Frying or broiling was not associated with the risk of EAC. Grilling/barbecuing was associated with a 50% non-significant elevated risk of EAC [90]. The ORs for barbecuing were 3.1. Broiling/frying pork or chicken was not associated with the risk of EAC. Even doneness preference was not strongly or monotonically associated with EAC risk [90]. Among the chemical compounds formed during the cooking process, acrylamide is one of those that potentially increases the risk of developing cancer for consumers in all age groups [141]. Acrylamide forms naturally in starchy food products subjected to high-temperature cooking (>120°C) such as frying, baking, and roasting. In our review, only one retrieved case-control study [37] showed that the adjusted risk of EAC was higher (OR 1.28; 95% CI 0.75-2.17), but not significant, among participants in the highest quartile of acrylamide exposure (≥44.08 μg/day) compared to the lowest (<27.27 μg/day). The risk was higher among overweight or obese people with a high intake (OR 2.09; 95% CI 0.97-4.53). However, no dose-response association was observed [37].

Heterocyclic amines (HCAs) are the other chemicals formed during the cooking process which seem to increase cancer risk in humans. These compounds are mainly formed in meat and fish cooked at high temperatures. HCAs are formed in greater quantities when meats are overcooked or blackened [142]. No conclusive results were obtained in our review for HCAs and the risk of EAC. In a 2003 Swedish nationwide, population-based case-control study with 185 EAC patients, Terry et al. [85] did not find any association between a dietary intake of HCAs and EAC risk. In 2011, Cross et al. [101] found a positive association between HCA intake and EAC. In particular, a borderline statistically significant increased risk of EAC was found for those with the highest intake (25 ng/1000 Kcals) of MeIQx (2-amino-3, 8-dimethylimidazo [4,5-f] quinoxaline) and the highest intake (127.3 ng/1000 Kcals) of PhIP (Pyridine) (HR 1.35, 95% CI 0.97–1.89, p for trend = 0.022; HR 1.45, 95% CI 0.99–2.12, p for trend = 0.463, respectively).

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3.7 Alcohol

Alcohol and alcoholic beverages are carcinogenic substances (group 1) for humans, as the International Agency for Research on Cancer declared in 2009 [143]. "Limit alcoholic drinks" is the WCRF recommendation [10]. Although the link between alcohol intake and many cancers are well established, the association between EAC and alcohol consumption is not completely clear. In fact, it is particularly hard to distinguish the possible effect due to dosage, duration, frequency of alcohol intake, and possible patient behavioral changes after diagnosis. In our review, we found 11 case-control studies [88, 37, 47, 49, 54, 63, 77, 95, 46, 48, 31], 6 cohort [127, 98, 110, 107, 113, 133], and 1 cross-sectional study [103] evaluating the association between alcohol intake and the risk of EAC. From among our 11 case-control studies, three of them found a statistically significant association between alcohol consumption and the risk of EAC. In particular, the studies conducted by Garidou et al. [48] and Chen et al. [37] show that consuming more than 5 drinks/day was a risk factor for EAC. Their results showed ORs that are 5 to 24 times higher in heavy drinkers (daily alcohol consumption >30ml/day) independent of the duration assumed [37], whereas EAC did not appear to be strongly associated with alcohol consumption in studies by Gao et al. [47] and Hashibe et al. [49]. The first author to find no association between alcohol intake and EAC was Lagergren et al. [54]. In this study, never users of alcohol had a higher risk of EAC compared to ever users. Beer and wine consumption was not associated with a risk of EAC, but users of hard liquor ran a low risk. This negative association, however, was not dose-dependent [54]. One year later, Wu et al.[95] also confirmed that excessive use of alcohol was not associated with the risk of esophageal adenocarcinoma, as did the prospective nested case-control study conducted by Lindblad et al. in 2005 [63]. Lastly, Pandeya et al. [77] found no evidence of an alcohol dose effect for EAC and no evidence of any association (linear or nonlinear) between average lifetime beer intake and risks of EAC. Inversely, the risks of EAC were reduced significantly among those with very low intakes of sherry or liqueur (<10 g/wk) and a low to moderate intake (<90 g/wk) of wine. The potential protective role of wine was previously found by Gammon et al. in 1997 [46]. However, these results were not confirmed in a prospective hospital-based case-control study[88]. Another author confirmed the absence of association in a 2009 large population-based case-control study in Ireland, while also evaluating the historical (at age 21 and 5 years before the interview date) total alcohol consumption (OR 0.75, 95% CI 0.46-1.22) [31].

Among the six cohort studies retrieved, Ji J. et al.[113] showed an increased risk of EAC (Standardized Incidence Ratio [SIR]=1.20, 95% CI 1.01-1.41) in subjects with a heavy alcohol intake; in contrast, Steevens J. et al.[127] found no association between alcohol intake (≥ 30g/day) and the risk of EAC (RR=1.04, 95% CI 0.54-2.02). Similar results were also found by Allen et al. [98] in their UK cohort study, according to which any alcohol intake threshold assessed (≤2; 3-6; 7-14; ≥15 drinks/week) was statistically significantly associated with the risk of EAC. Conversely, two articles [107, 110] did not find a statistical association, whereas Yates et al. [133] found an inverse association between alcohol intake and EAC risk.

3.8 Smoking

In addition to the ten cancer prevention recommendations, the WCRF/AICR report suggests 'not smoking and avoiding other exposure to tobacco' [10]. In our review, all the retrieved studies concur in defining smoking as an important risk factor for EAC [32, 37, 103, 44, 46-49, 63, 78, 127, 45, 76, 88, 93, 95, 136, 110], except in the study by Langergren et al. [54] where the association between tobacco smoking and the risk of EAC was weak or absent (OR was 1.10, 95% CI 0.60–2.20) among persons who had smoked more than 20 cigarettes daily for more than 35 years compared with never smokers. In particular, 2 studies found a higher risk of EAC among heavy smokers [37, 49]. ORs ranged between 2 to 4 in the case of ever smokers of more than 10 cigarettes per day. No gradients in risk were seen for the smoking duration; however, this data was disconfirmed by Chen et al. [37] (OR 3.65 for >30 years of smoking). Focusing on the relationship between smoking

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and two other confirmed risk factors for EAC, obesity and GERD, Whiteman et al. [93] and Pandeya et al. [78] respectively evaluated the relative risk. Even though smoking significantly increased the risk of EAC, there was no evidence of interaction with body mass. Among never smokers and those with a modest smoking history, risks of EAC were significantly higher in obese rather than non-obese people. There was no difference between heavy smokers as regards the risk of EAC in healthy, overweight, or obese subjects [93]. Relative risks of 2.5 for EAC were found for those who reported a 30+ pack-year smoking history, but no GERD symptoms. Those never smokers who reported GERD symptoms on at least a weekly basis had a markedly elevated relative risk of EAC.

The combined effects of GERD and smoking showed a 60% higher risk of EAC measured as a synergy index (*S*) (*S*= 1.6; 95% CI 0.80-3.00) [78]. Marked differences were found among users and non-users on evaluating the filter status. After an in-depth analysis on the type of smoke, Lagergren et al. [54] found an OR of 1.8 (95% CI 1.00, 3.40) among frequent pipe smokers when compared with never smokers. Cigar smoking was not associated with the risk. There was a declining risk with time since cessation of smoking (p for trend=0.020). Snuff users had an OR of 1.2 (95% CI 0.80–1.90) for EAC compared with never users. Those using 15–35 quids per week showed a statistically significant 2-fold increase in risk when compared with never users.

We found controversial results with regard to the potential protective effect of smoking cessation. In Wu et al. [95], the risk of EAC remained significantly elevated among former smokers who had quit smoking 10-19 years earlier (OR 1.70, 95% CI 1.10-2.90). Respective ORs (and 95% CIs) associated with being a former and current smoker compared to a never smoker were 1.50 (95% CI 1.00-2.30) and 2.7 (95% CI 1.60-4.40), respectively. Similar results were also found by Freedman et al. in a prospective study considering both current and former smokers [105]. In their case-control study, Pandeya et al. found that the 'time since quitting' was independently associated with an approximate 15% reduction in risk per decade [76]. In Whiteman et al. [93], the analysis of smoking status (never, former, current) resulted in associations of similar magnitude (EAC: former smokers OR 1.50, 95% CI 1.10-2.10; current smokers OR 2.30, 95% CI 1.50-3.50). A significant 2-fold increase in risk was found among previous smokers and among persons who had been smoking for more than 35 years [54]. Gao et al. and Lindblad et al. also estimated the risk of EAC according to gender. Gao et al. [47] found a 60% higher risk for women than for lifelong non-smokers. Lindblad et al. [63] did not find significant differences between men and women. Passive smoking is another important risk factor for different types of diseases. Duan et al. [44] evaluated the risk of EAC in a study involving non-smokers exposed to passive smoking during childhood. These subjects did not show a higher level of EAC risk than those with no exposure to passive smoking. Exposure to passive smoking during adulthood was associated with a raised risk of EAC (adjusted OR 1.80, 95% CI 0.81–4.00); an increased risk of EAC was also observed in adults who were exposed to passive smoking for a long time [44].

Our investigation also included two cohort studies that had analyzed tobacco use and EAC risk [127, 136]. Both concur in considering smoking as a real risk factor. Current and former smokers have an increased risk of EAC compared to never smokers. Smokers (current and former) who use cigarettes have a higher risk (RR 2.60, 95% CI 1.50-4.30) than those who only smoke cigars (RR 1.20, 95% CI 0.20-0.93) or a pipe (RR 1.50, 95% CI 0.50-2.40) [136]. In Steevens et al., the association between the frequency of cigarette smoking and the risk of EAC was statistically significant (p trend=0.010), with a statistical significance ($p<0.05$) for 10 and 20 years after smoking cessation [127]. The risk of EAC did not increase for moist snuff users [136].

3.9 Interaction between smoking and alcohol

This section evaluates the possible synergic effect of tobacco and alcohol on EAC. We found a total of 5 case-control studies and three of them did not find a synergic effect for any of the smoking strata [37, 49, 77]. Inversely, in Gao et al.[47], the risk tended to rise with increasing alcohol intake within each smoking category, except for non-smokers, and

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with increasing smoking levels within each alcohol category, including non-drinkers. The combined effect of smoking and drinking alcohol was pronounced among men; the OR for those who smoked more than 1 pack per day and drank more than 750 g of ethanol per week was 12.0 (95% CI 6.60-22.10). Lagergren et al. [54] also found a smaller but still significant risk with an OR of 2.30 (95% CI 0.90–5.70).

3.10 Socioeconomic factors and EAC risk

In 2006, Veugelers et al. [88] did not find a statistically significant association between educational level and EAC risk; to the contrary, in 1997, Gammon et al. [46] found that a high educational level has a protective effect; the same also holds true for income level. In 2005, Jansson et al. [52] found a statistical association between socioeconomic status and EAC in a crude model, which was no longer significant after adjustment for BMI, reflux, and smoking habits. They also found the same results for educational level and for living in urban instead of rural areas. Interesting, however, is the statistically significant association between EAC and the number of cohabitants. Single people had twice the increased risk of EAC compared to those who had a partner [52].

4. Discussion

To the best of our knowledge, this is the first systematic review providing a comprehensive overview of different types of lifestyles related to EAC risk alone. We carefully excluded all studies analyzing a combination of EAC and ESCC, and EAC combined with gastric cardia adenocarcinoma. According to our results, weight control is an important factor in the prevention of EAC. Indeed, BMI is unanimously defined as an independent risk factor for EAC that does not appear to be associated with GERD. A higher than normal BMI (≥25.0 kg/m^2) is significantly and progressively associated with an increased risk of EAC, as is body weight and waist circumference alone. These results, confirmed in all analyzed studies independently of study design [144-146], highlight the importance of maintaining anthropometric parameters within normal values (BMI 18.0 – 24.9 kg/m^2; WC: woman <80.0 cm; man <94.0 cm) in both males and females. Moreover, the higher the BMI, the higher the risk of EAC [146]. Furthermore, BMI>30 kg/m^2 was most strongly associated with early-onset (<50y) EAC (OR 4.19, 95% CI 2.23, 7.87), and with significant differences across age groups (p effect modification= 0.042). The magnitude of the association was higher in early-onset EAC than in later-onset patients. ORs for the other age categories ranged between 2.6 and 2.8 [147]. We can conclude that the elevated risk related to a high BMI probably represents a causal effect.

Even though the beneficial effect of physical activity is well known, EAC does not appear to be positively affected by physical activity. Indeed, our review only resulted in one population-based case-control study showing an inverse association between the total amount of physical activity and the risk of EAC [89].

In contrast, nutrition appeared to play a crucial role in EAC prevention. Although it is not easy to precisely assess dietary intake and to homogenously define dietary patterns, our results, in accordance with previous meta-analyses of observational studies [148], suggest that the "western dietary pattern" — typically poor in vegetables, legumes and whole grains and high in red meat and especially processed meat — is associated with an increased risk of EAC. However, there appears to be conflicting results in studies that focused on meat consumption. Indeed, it is not unanimously affirmed, even if most of the included studies found an increased risk of EAC in subjects with a high consumption of meat (particularly red and processed meat). These contrasting results could be due to the intrinsic limitation of single studies where the total sample size is generally limited. Subsequent meta-analyses consistently found an increased risk of EAC for a high intake of meat, considering both total meat intake [149] and red and processed meat [150] [151] in both case-control and cohort studies. Additionally, the meta-analysis conducted by Huang et al. [151] assessed the risk of red and processed meat separately and, also in this case, results confirmed an increased risk of EAC for the highest intake compared to the

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lowest, which is slightly higher for processed meat consumption [RR 1.41 (95% CI 1.09–1.83)] as opposed to red meat consumption [RR 1.31 (95% CI 1.05–1.64)]. High risk was also confirmed in the dose-response analysis, which showed a higher risk [RR 1.45 (95% CI 1.09–1.93)] per 100 g/day of red meat intake and per 50 g/day of processed meat intake [1.37 (95% CI 1.03–1.81)] [151]. On analyzing other animal products, we found no association between fish and EAC risk, as described in Han et al. [152] and Zhu et al. [149].

By contrast, the results of studies included in our systematic review suggest that a "healthy dietary pattern" rich in fruit, vegetables and whole grains has a protective role, as opposed to a diet rich in animal fat, meat, processed meat, fried, or salty foods. Based on this growing evidence, we can hypothesize that a "healthy dietary pattern" is characterized by a high dietary intake of fiber. In actual fact, fiber intake has a biologically plausible explanation in cancer prevention [19, 153, 154], including EAC prevention through the binding of possible carcinogens, removing damaged cells from the esophageal epithelium [155-157], and positively modifying esophageal microbiota [158]. Moreover, *in vitro* studies also demonstrated a possible direct role of fiber in promoting apoptosis and inhibiting cell growth, even among esophageal adenocarcinoma cells (cell lines) [159]. Furthermore, fiber in food is associated with several bioactive compounds, such as polyphenols, that could have positive effects on modulating inflammation and reducing pro-inflammatory cytokine interleukin-6 concentrations [160].

In man, it is associated with reduced gastroesophageal reflux symptoms, glycemic response, gastric emptying and overall calorie intake helping in weight control [161, 155, 162]. Studies included in our review demonstrated the protective role of foods of plant origin (fruit and vegetables), in line with previous meta-analyses [86, 163] which estimated a risk reduction of 24% and 27%, respectively, for the highest intake of vegetables and fruit, and approximately 30% for a combination of the two. The protective role of fruit and vegetables is probably due not only to the fiber amount, but also to the vitamin and antioxidant compound intake [163]. Although the meta-analysis showed the protective effect of fiber intake, there was a high statistical heterogeneity. The high heterogeneity is probably due to the unquantified fiber intake in the majority of included studies, such as the recall bias intrinsic in primary studies and the inclusion of case-control studies instead of cohort studies (which are known to be superior to case-control). Indeed, fruit and vegetables contain an important amount of both vitamins and antioxidants, which appear to be much more effective than supplements. Our results are in line with a previous meta-analysis which reported a 50% lower risk of EAC (OR 0.49, 95% CI 0.39-0.62) in subjects with a high intake of dietary vitamin C, with a dose effect at high intake [164]. With regard to vitamin E, a meta-analysis found a slight but non-significant reduction in EAC risk [164]. However, the results of our systematic review highlight that dietary vitamin intake is much more effective than vitamin supplementation, with the exception of iron and folic acid. This important phenomenon is probably due to the possible interactions and synergistic combinations of the several bioactive compounds contained in vegetables instead of "pills", which still remain extremely useful in the case of clearly diagnosed deficiencies.

As described in previous studies, cooking methods may be related to an increased risk of upper gastrointestinal tract cancers [165-167, 85]. According to WCRF/AICR recommendations, cooking methods that typically involve high temperatures (such as grilling, baking, and frying) can lead to a variety of potential carcinogens [168]. Baked or fried potatoes, bread (crisp or soft), cookies and coffee can particularly contribute to an increased dietary acrylamide intake. Cooking meat at high temperatures can give rise to the formation of PAHs and HCAs [169, 170]. These compounds have been suggested to increase the total risk of esophageal cancer [171, 172, 85]. Our review revealed a positive, but non-statistically significant, trend between the daily intake of acrylamide and EAC risk, and mostly in obese patients. HCAs may also play a role in increasing the risk of EAC, but the positive trend that we found was not statistically significant.

With reference to non-alcoholic beverage consumption, we found contrasting results when both (carbonated) soft drinks and the hot beverages, coffee and tea, were considered. We do not have a clear idea of the reasons behind this; however, it could be due to

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the intrinsic limitations of the studies since these are based on surveys and can be affected by several biases including a social desirability bias, recall bias, or dietary assessment performed after diagnosis and which may not reflect intake in the distant past. When it comes to coffee and tea, the contrasting results can also be explained given that these drinks are rich in flavanols and flavonols which have been demonstrated to have anticarcinogenic effects [173]. Caffeine is a well-known factor capable of reducing esophageal sphincter contraction (a cause of reflux) [174].

Tobacco and alcohol are two of the main risk factors causing several types of cancer. We analyzed the link between alcohol and EAC and tobacco and EAC separately, and the interaction between alcohol and smoking on EAC risk. Although alcohol consumption is linked to cancer of the oral cavity, pharynx, esophagus, liver, colorectal, and breast in women, it does not seem to be related to EAC [175-177]. Contrasting results were also found when considering alcoholic beverages. Even if some meta-analyses found a significant association between a lower alcohol intake and EAC [178, 179], no dose-response effect was found. Moreover, we failed to find clear evidence that any particular type of beverage (beer, liquor, or wine) was especially associated with an increased or decreased cancer risk, as also confirmed by the Tramacere et al. meta-analysis [180]. With regard to smoking habits, data in our review suggest that smokers, particularly heavy smokers, are at high risk of EAC. This evidence is in line with two pooled analyses which also confirmed a consistent dose-response association [181, 178]. Risk also seems to persist in former smokers, as confirmed in a pooled analysis [181] and in a meta-analysis of 13 studies (9 case-control and 4 cohort), where the risk for former smokers was lower compared to current smokers, but was still present after smoking cessation.

4.1 Strengths and limitations

Even though this systematic review offers an extensive overview of the potential relationship between EAC and several lifestyles, there are some limitations with regard to both the included studies and the review *per se*. We only included observational epidemiological studies that assessed the relationship between certain human behaviors (smoking habits, nutrition status, food habits, etc.) and health outcomes, in particular EAC risk [182]. In the majority of included studies, food intake was assessed through an FFQ evaluating dietary habits before cancer diagnosis. This aspect needs to be taken into account because of possible recall bias. Recall bias is a systematic error resulting from the imperfect recall of exposure, particularly true in retrospective studies [183]. Nevertheless, the FFQ appears to be one of the best methods to measure historical exposures. In the majority of studies, the FFQ was administered by an interviewer, which increases the quality and accuracy of data gathered. Our review's limitations include the language filter, since we only included articles published in English, which could introduce potential bias. Excluding languages other than English may introduce a language bias and lead to the exclusion of some relevant studies [184]. We performed a structured computer search on two databases, as recommended by international guidelines. Taking into account the type and the nature of the search question, we believe that it covered the majority of relevant potential sources of evidence, especially because our study aimed to offer an updated summary of the evidence-based literature available to improve the statements' consistency [185]. Moreover, the broad inclusion criteria allowed us to include different areas of interaction between potential risk factors and EAC [185]. Lastly, the quality of included studies was generally high. More specifically, the vast majority of cohort studies obtained the highest score compared to case-control studies. Consequently, it can be concluded that our results are reliable, being based on solid and, on average, coherent evidence.

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5. Conclusions

This systematic review selectively evaluated the impact of several life style patterns on EAC risk. Despite the wealth of available literature on esophageal cancer and associated risk factors, such as the last update on esophageal cancer published by the WCRF Continuous Update Project in 2018, no extensive overview focusing solely and specifically on EAC is available [10]. This systematic review leads us to suggest that no single specific food is able to prevent disease (EAC), but rather a lifestyle pattern which takes into consideration other factors besides diet. An important factor is the socioeconomic status, which is strictly related to diet and environmental exposure. In fact, descriptive epidemiology suggests a positive trend in EAC incidence, particularly in high-income countries. Certain areas, such as salty food and EAC specifically, were also not explored or the study's results are not conclusive, as in the case of alcohol intake and EAC.

Primary prevention remains the best option for esophageal adenocarcinoma. We need to provide patients and the high-risk population with comprehensible and easy to follow recommendations. Anthropometric measurements such as body weight, BMI, and abdominal circumference, along with a reduction in red meat and processed meat consumption, an increase in plant food consumption and the avoidance of smoking and excessive alcohol consumption, should be the crucial points on which to focus efforts for esophageal adenocarcinoma prevention. Future investigations should mainly focus on the association between carbonated drinks and the risk of EAC, the dietary intake of vitamins such as vitamin D and calcium, as well as cooking processes and chemical modifications during cooking.

Supplementary Materials: Table S1: Quality assessment of case-control studies, using the Newcastle-Ottawa Scale (NOS), in alphabetical order. Table S2: Quality assessment of cohort studies, using the Newcastle-Ottawa Scale (NOS), in alphabetical order

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