MINI REVIEW

Barrett’s esophagus, esophageal and esophagogastric junction adenocarcinomas: The role of diet

Endobrachyœsophage, adénocarcinome de l’œsophage et de la jonction œsogastrique: le rôle de la nutrition

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Available online 20 October 2010

Summary  Identification of modifiable risk factors is an attractive approach to primary prevention of esophageal adenocarcinoma (EAC) and esophagogastric junction adenocarcinoma (EGJAC). We conducted a review of the literature to investigate the association between specific dietary components and the risk of Barrett’s esophagus (BE), EAC and EGJAC, supposing diet might be a risk factor for these tumors. Consumption of meat and high-fat meals has been found positively associated with EAC and EGJAC. An inverse association with increased intake of fruit, vegetables and antioxidants has been reported but this association was not consistent across all studies reviewed. Few studies have examined the association between diet and BE. Additional research is needed to confirm the aforementioned association and clarify the mechanisms by which dietary components affect the risk of developing EAC and EGJAC. Future studies could advance our knowledge by emphasizing prospective designs to reduce recall bias, by using validated dietary intake questionnaires and biological measures and by considering important confounders such as gastro-esophageal reflux disease (GERD) symptoms, tobacco and alcohol use, biometrics, physical activity, and socioeconomic factors.

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Résumé  L’identification de facteurs de risque susceptibles d’être modifiés, représente une stratégie intéressante dans la prévention primaire de l’adénocarcinome de l’œsophage (AO) et de la jonction œsogastrique (AJO). Nous avons révisé la littérature pour analyser l’association entre certaines composantes nutritionnelles et le risque de développer l’endobrachyœsophage (EBO), l’AO et l’AJO. Une importante association a été retrouvée entre la consommation de
viande et de produits riches en gras et le risque de développer l’AO et l’AOJ. D’autres études identifiées une corrélation inverse avec une alimentation riche en fruits, légumes et antioxydants, même si cette association n’était pas consistante dans tous les études. Très peu d’études ont analysé l’association entre nutrition et EBO. D’ultérieures recherches seront nécessaires pour confirmer cette association et éclaircir les mécanismes par lesquels les composantes nutritionnelles peuvent affecter le risque de développer l’AO et l’AOJ. Ulitères études perspectives pourront améliorer notre connaissance en réduisant les biais d’information, avec l’usage de questionnaires nutritionnels préalablement validés, des tests biologiques de mesures et en considérant d’autres facteurs confondants comme les symptômes liés au reflux, la consommation de tabac et d’alcool, la biométrie, l’activité physique et les facteurs socioéconomiques.

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Introduction

The incidences of esophageal adenocarcinoma (EAC) and esophagogastric junction adenocarcinoma (EGJAC) have risen dramatically in Western countries since the 1970s while rates for esophageal squamous cell carcinoma (ESCC) and non-cardia gastric adenocarcinoma (AC) have remained stable or decreased [1,2]. EAC and EGJAC are located in anatomic proximity and may have similar epidemiologic characteristics that make them different from ESCC and from AC of the more distal stomach [3]. Common features include high male/female ratios (7:1) and a higher incidence among Whites than among Blacks [1,4]. In contrast, differences in the etiologies, demographics, and geographic distributions have also been reported between EAC and EGJAC [5—7].

Barrett’s esophagus (BE) is the most established risk factor for the development of EAC and EGJAC. BE is an acquired condition related to long-standing gastro-esophageal reflux disease (GERD) in which normal squamous epithelium is replaced by metaplastic columnar epithelium [8]. Approximately 10% of patients with frequent GERD develop BE, and 0.5—1.0% per year of them will be diagnosed with EAC [10,9]. There may be a familial predisposition in the onset of BE and EAC/EGJAC [11,12]. Familial clusters of BE and EAC have been reported, and an autosomal dominant inheritance has been proposed [13—16]. However, familial clusters do not account for the majority of BE and EAC/EGJAC cases observed.

Environmental risk factors for BE and EAC/EGJAC have also been investigated [12,17]. Identifying and intervening on modifiable environmental risk factors, such as diet, may aid in the prevention of the cancers.

We conducted a review of the literature to investigate the association between specific dietary components and the risk of BE, EAC and EGJAC.

Material and methods

Search strategy

We searched PubMed for all articles published between 1990 and March 2010, using the medical subject healings (MeSH) or keywords “Barrett’s (o)esophagus” combined with the following terms: diet, food, (diet AND [fruit OR vegetable]), (diet AND [fat OR meat]), (vitamin OR selenium OR antioxidant). Similar searches were performed using “(o)esophag* AND (adenocarcinoma OR cancer OR carcinoma)” and “gastric cardia AND (adenocarcinoma OR cancer OR carcinoma)”, each combined with previous mentioned terms.

Study selection

Studies were included if they met the following inclusion criteria:

- published in English language;
- epidemiologic studies evaluating the relationship between dietary components and risk of BE and/or cancer.

Exclusion criteria included:

- combined ESCC and AC as a single outcome;
- combined gastric cardia carcinoma and gastric non-cardia carcinoma as a single outcome;
- only considered ESCC;
- experimental animal models;
- genetic or immunohistochemical studies.

A manual search of references list in the identified articles was also performed.

Results

Search results

The search terms identified a total of 347 published manuscripts. Excluding duplicates and studies not fulfilling inclusion/exclusion criteria, 80 studies were identified based on inspection of the title and the abstracts. Twenty-six studies were found using the MeSH term Barrett; 47 using [(o)esophag* AND [adenocarcinoma OR cancer OR carcinoma]] and seven using (gastric cardia AND [adenocarcinoma OR cancer OR carcinoma]).

The full text of all 80 articles was reviewed. Fourteen studies were reviews, two reviews + meta-analysis, one meta-analysis, 48 case-controls, 10 cohort, one ecologist, one comparative, one prospective, two cross sectional studies.

Forty-five studies investigated the association of BE/EAC/EGJAC and diet: eight reviews; one review + meta-analysis; one meta-analysis; 28 case-controls (23...
### Table 1  Barrett’s esophagus and diet.

<table>
<thead>
<tr>
<th>Author</th>
<th>Location</th>
<th>Design</th>
<th>Subjects number</th>
<th>Type of nutrient</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veugelers et al. (2006)</td>
<td>Canada</td>
<td>Population-based case-control study</td>
<td>130 BE; 57 EAC; 102 PC; 142 GERD C</td>
<td>Vitamin C</td>
<td>↓ BE    ↓ EAC</td>
</tr>
<tr>
<td>Anderson et al. (2007)</td>
<td>Ireland</td>
<td>Population-based case-control study</td>
<td>224 BE; 227 EAC; 260 PC</td>
<td>V + F, Fruit, Vegetables</td>
<td>↓ BE    ↓ EAC  ↓ EAC</td>
</tr>
<tr>
<td>Kubo et al. (2008)</td>
<td>USA</td>
<td>Population-based case-control study</td>
<td>296 BE; 309 PC; 308 GERD C</td>
<td>Antioxidants, V + F, Vitamin supplement use</td>
<td>↓ BE    ↓ BE  ↓ BE</td>
</tr>
<tr>
<td>Kubo et al. (2008)</td>
<td>USA</td>
<td>Population-based case-control study</td>
<td>296 BE; 309 PC; 308 GERD C</td>
<td>V + F, non fried fish (health-conscious DP) Fast food and meat (Western DP)</td>
<td>↓ BE    ↑ BE  ↑ BE</td>
</tr>
<tr>
<td>Kubo et al. (2009)</td>
<td>USA</td>
<td>Population-based case-control study</td>
<td>296 BE; 309 PC</td>
<td>Omega-3-fatty-acids, polyunsaturated fat, fiber, V + F, meat Trans-fat, processed foods and fast foods</td>
<td>↓ BE    ↓ BE  ↑ BE</td>
</tr>
<tr>
<td>Thompson et al. (2009)</td>
<td>USA</td>
<td>Population-based case-control study</td>
<td>170 BE; 182 PC</td>
<td>Vegetables, V + F</td>
<td>↓ BE</td>
</tr>
<tr>
<td>Mulholland et al. (2009)</td>
<td>Ireland</td>
<td>Population-based case-control study</td>
<td>220 BE, 224 EAC; 256 PC; 219 GERD C</td>
<td>Fiber, carbohydrate Dietary glicemic index</td>
<td>↓ BE      ↓ EAC  ↓ EAC</td>
</tr>
</tbody>
</table>

↓: decreased risk; ↑: increased risk; NS: not significant; /: not correlated; BE: Barrett’s esophagus; EAC: esophageal adenocarcinoma; PC: population controls; GERD C: gastro-esophageal reflux disease controls; V + F: vegetables and fruit; DP: dietary pattern.
population-based and five hospital-based); six cohort and one ecologist studies.

Three studies investigated serum antioxidants concentrations in BE patients: two cross sectional and one prospective cohort studies.

**Barrett’s esophagus**

Few data exist on the association between diet and BE (Table 1).

An inverse relationship between fruits, vegetables and antioxidants intake and the risk of developing BE has been reported, although higher doses of antioxidants from vitamin supplements did not reduce the risk beyond dietary intake [18–23]. The association between lower risk of BE and fruit and vegetable intake is weaker after adjusting for GERD symptoms [22].

On the other hand, a diet rich in meat and fast food moderately increased the risk of BE compared to population controls, but was not a risk factor for BE among individuals with GERD [19]. Cooking methods of meat did not influence the risk of BE. An unexpected inverse association between meat and long segment BE was described. This association remained after adjusting for GERD [24].

Significantly lower plasma concentrations of antioxidants such as selenium, vitamin C, β-cryptoxantin and xanthophylls have been found in BE patients compared with patients without BE (esophageitis and controls groups) [25]. In another study dietary selenium, but not other antioxidants, was inversely associated with neoplastic progression in BE patients [26].

**Cancers of the esophagus and esophagogastric junction**

**Antioxidants, vitamins, fruits and vegetables, fiber**

The major sources of dietary antioxidants are fruit and vegetables (Table 2). The most protective effect was attributable to red-orange (carrots, tomatoes) and dark green (spinach, chard) vegetables, berry juice, apples and citrus fruit [27]. Antioxidants may protect against oxidative/nitrosative stress by binding with reactive oxygen species. Oxidative/nitrosative stress has been implicated in many human diseases, including cancer [28,29]. In BE patients the inflammation caused by chronic GERD can result in the production of free radicals promoting carcinogenesis via direct DNA damage and inhibition of apoptosis [30].

Several studies have evaluated antioxidants intake in patients with EAC using dietary questionnaires [3,27,31–38], while there are few publications on antioxidants specifically in populations of patients with BE [18,20,37].

In a population-based case-control study, Terry et al. observed that higher dietary intake of antioxidants (vitamin C and β-carotene more than α-tocopherol) was associated with a 50% risk reduction for EAC, in particular in subjects under presumed higher oxidative stress due to GERD. No additional reduction in the risk was observed in subjects taking vitamin supplements and no association with the risk of EGJAC was found [34]. These results are different from cohort study by Dong et al., in which the use of one or more vitamin supplement in BE patients was associated with a 62% decreased risk of EAC [37]. A meta-analysis also did not support a consistent association between antioxidant intake and risk of cardia AC. Furthermore, some studies even suggested an increased risk of EGJAC associated with higher intake of vitamin C and E [7,34,36].

Serum selenium levels has been inversely correlated with the risk of EAC among BE patients, but beyond a threshold of approximately 1.5 μg/L a further increases in serum selenium levels has no additional benefit in decreasing the risk of progression toward EAC [39].

The efficacy of antioxidant supplements in decreasing the incidence of gastrointestinal cancer is contradictory. Bjelakovic et al. in a systematic review of antioxidants supplements found no evidence of a protective effect against gastrointestinal cancers. On the contrary, with the possible exception of selenium, they seem to increase overall mortality. In addition, β-carotene and vitamin A supplements seem to increase the cancer risk [40–42]. A balanced diet typically contains safe levels of antioxidants vitamins and trace elements, while the use of supplements might cause excessive suppression of the free radicals leading to adverse health consequences [43].

Conflicting results of vegetable and fruit intake on BE progression, and development of EAC and EGJAC have been published [22,31,32,44–58].

A meta-analysis of the effect of fruits and vegetables on cancer risk showed discrepancies between the overall results of case-controls and cohort studies [59]. In a prospective cohort study, total fruit and vegetable intake was not significantly associated with EAC. Analyzing the intake of vegetables and fruit separately, a significant protective association between EAC risk and intake of Chenopodiaceae (spinach) was found [56]. Another prospective cohort study, EPIC-EUROGAST, also did not support a significant protective effect of fruits and vegetables on cancer risk [53].

Data from case-control studies support that total fiber intake was inversely associated with risk of EAC and EGJAC. These associations remained after adjustment for dietary fat and other non-dietary factors including *Helicobacter pylori* infection, body size, smoking and GERD [23,31–33,45,46,48,55,57,60]. When analyzed separately, a stronger inverse association has been noted for EGJAC than for EAC, which had no statistically significant association with high dietary fiber. In particular, the lower risk of EGJAC was only associated with a high intake of cereal fiber. There was no risk reduction found with fiber intake from vegetables and fruit. These differences may be due to the nitrite scavenging action of lignin present in cereal fiber and absent in fiber from fruit and vegetables [60].

**Fat and meat**

Conflicting results concerning meat, fat and dairy product intake and the risk of developing EAC/EGJAC have been reported (Table 2). In the European EPIC prospective study, the overall intake of red or processed meat was not associated with the risk of EGJAC, while a positive but non-statistically significant association was reported with EAC. The increased risk was noted with gastric non-cardia AC, especially in *H. pylori* antibody positive subjects [61].
Table 2  Nutritional factors in patients with EAC/EGJAC.

<table>
<thead>
<tr>
<th>Author</th>
<th>Location</th>
<th>Design</th>
<th>Subjects number</th>
<th>Type of nutrient</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palli et al. (1992) [44]</td>
<td>Italy</td>
<td>Population-based case-control study</td>
<td>68 EGJAC; 1159 PC</td>
<td>Raw V, fresh F, citrus, vitamin C, Meat, protein, cholesterol, soup, salty foods</td>
<td>↓ EGJAC, ↑ EGJAC</td>
</tr>
<tr>
<td>Kabat et al. (1993) [31]</td>
<td>USA</td>
<td>Hospital-based case-control study</td>
<td>173 males (EAC/EGJAC); 4544 males PC</td>
<td>Fiber, vitamin A from plant sources, Fat, vitamin A from animal sources</td>
<td>↓ EAC/EGJAC, ↑ EAC/EGJAC</td>
</tr>
<tr>
<td>Brown et al. (1995) [45]</td>
<td>USA</td>
<td>Population-based case-control study</td>
<td>174 males EAC; 750 PC</td>
<td>Raw V + Fd, fiber, Fat, coffee, tea</td>
<td>↓ EAC, NS EAC</td>
</tr>
<tr>
<td>Tzonou et al. (1996) [32]</td>
<td>Greece</td>
<td>Hospital-based case-control study</td>
<td>56 EAC; 200 PC</td>
<td>V + F, fiber, vitamin A, C, Added oil and fat, polyunsaturated fat</td>
<td>↓ EAC, ↑ EAC</td>
</tr>
<tr>
<td>Zhang et al. (1997) [33]</td>
<td>USA</td>
<td>Hospital-based case-control study</td>
<td>95 (EAC/EGJAC); 132 PC</td>
<td>Fiber, vitamin B6, A E, folate, minerals, High dietary calories, fat</td>
<td>↓ EAC/EGJAC, ↑ EAC</td>
</tr>
<tr>
<td>Cheng et al. (2000) [46]</td>
<td>UK</td>
<td>Population-based case-control study</td>
<td>74 females EAC; 74 females PC</td>
<td>Fruit</td>
<td>↓ EAC</td>
</tr>
<tr>
<td>Terry et al. (2000) [34]</td>
<td>Sweden</td>
<td>Population-based case-control study</td>
<td>185 EAC; 258 EGJAC; 815 PC</td>
<td>Vitamin C, β-carotene, α-tocopherol</td>
<td>↓ EAC/EGJAC</td>
</tr>
<tr>
<td>Ekström et al. (2000) [27]</td>
<td>Sweden</td>
<td>Population-based case-control study</td>
<td>74 EGJAC; 1165 PC</td>
<td>Vitamin C, E, V + F, β-carotene</td>
<td>↓ EAC, NS EGJAC</td>
</tr>
<tr>
<td>Terry et al. (2001) [47]</td>
<td>Sweden</td>
<td>Population-based case-control study</td>
<td>185 EAC; 258 EGJAC; 815 PC</td>
<td>V + F</td>
<td>NS ↓ EAC/EGJAC</td>
</tr>
<tr>
<td>Terry et al. (2001) [60]</td>
<td>Sweden</td>
<td>Population-based case-control study</td>
<td>185 EAC; 258 EGJAC; 815 PC</td>
<td>Total fiber; cereal fiber, Fiber from V + F</td>
<td>NS ↓ EAC, ↓ EGJAC/EGJAC</td>
</tr>
<tr>
<td>Wolfgarten et al. (2001) [48]</td>
<td>Germany</td>
<td>Population-based case-control study</td>
<td>EAC 40; 100 PC</td>
<td>V + F, dietary fiber, carbohydrates, Protein, fat, milk</td>
<td>↓ EAC, ↑ EAC</td>
</tr>
<tr>
<td>Chen et al. (2002) [51]</td>
<td>USA</td>
<td>Population-based case-control study</td>
<td>124 EAC; 449 PC</td>
<td>Dietary fiber, carbohydrates, carotenoids, vitamins, Saturated fat</td>
<td>↓ EAC, ↑ EAC</td>
</tr>
<tr>
<td>Chen et al. (2002) [49]</td>
<td>USA</td>
<td>Population-based case-control study</td>
<td>124 EAC; 449 PC</td>
<td>V + F, dairy products, fish, dark bread, Gravy</td>
<td>↓ EAC, ↑ EAC</td>
</tr>
<tr>
<td>Author</td>
<td>Location</td>
<td>Design</td>
<td>Subjects number</td>
<td>Type of nutrient</td>
<td>Results</td>
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<tr>
<td>Bollschweiler et al. (2002) [35]</td>
<td>Germany</td>
<td>Hospital-based case-control study</td>
<td>47 males EAC; 50 males PC</td>
<td>β-carotene, vitamin C, E, and folic acid</td>
<td>↓ EAC</td>
</tr>
<tr>
<td>Engel et al. (2003) [50]</td>
<td>USA</td>
<td>Population-based case-control study</td>
<td>293 EAC; 261 EGJAC; 695 PC</td>
<td>V + F</td>
<td>↓ EAC; ↓ EGJAC</td>
</tr>
<tr>
<td>Cai et al. (2003) [52]</td>
<td>China</td>
<td>Population-based case-control study</td>
<td>191 EGJAC; 222 PC</td>
<td>V + F, Salty fish, pickled vegetable</td>
<td>↓ EGJAC; ↑ EGJAC</td>
</tr>
<tr>
<td>Nouraie et al. (2005) [36]</td>
<td>Finland</td>
<td>Prospective cohort study</td>
<td>57 EGJAC; 27,110 PC</td>
<td>Retinol α-tocopherol, γ-tocopherol Vegetables, fruit</td>
<td>↓ EGJAC; ↑ EGJAC; /EGJAC</td>
</tr>
<tr>
<td>González et al. (2006) [53]</td>
<td>Europe (EPIC)</td>
<td>Prospective cohort study</td>
<td>65 EAC; 521,457 PC</td>
<td>V, citrus</td>
<td>NS ↓ EAC</td>
</tr>
<tr>
<td>González et al. (2006) [61]</td>
<td>Europe (EPIC)</td>
<td>Prospective cohort study</td>
<td>65 EAC; 521,457 PC</td>
<td>Total, red and processed meat</td>
<td>/EGJAC; NS ↑ EAC</td>
</tr>
<tr>
<td>Bahmanyar et Ye (2006) [54]</td>
<td>Sweden</td>
<td>Population-based case-control study</td>
<td>185 EAC; 258 EGJAC; 815 PC</td>
<td>V + F, fish, poultry, tomato Processed, red meat, sweets, high-fat dairy, and high-fat gravy</td>
<td>NS ↓ EAC; ↓ EGJAC; ↑ EAC; ↑ EGJAC</td>
</tr>
<tr>
<td>Wu et al. (2007) [55]</td>
<td>USA</td>
<td>Population-based case-control study</td>
<td>206 EAC; 257 EGJAC; 1308 PC</td>
<td>Fiber Fat, meat</td>
<td>↓ EAC; ↓ EGJAC; ↑ EAC; ↑ EGJAC</td>
</tr>
<tr>
<td>Freedman et al. (2007) [56]</td>
<td>USA</td>
<td>Prospective cohort study</td>
<td>198 EGJAC; 490,802 PC</td>
<td>V + F</td>
<td>/EAC</td>
</tr>
<tr>
<td>Dong et al. (2008) [37]</td>
<td>USA</td>
<td>Prospective study</td>
<td>339 BE; 37 EAC</td>
<td>Supplemental vitamins and minerals</td>
<td>↓ EAC</td>
</tr>
<tr>
<td>Navarro Silvera et al. (2008) [57]</td>
<td>USA</td>
<td>Population-based case-control study</td>
<td>282 EAC; 255 EGJAC; 687 PC</td>
<td>Fruit, vegetables, V + F Meat, grains, high-fat dairy</td>
<td>↓ EAC;/EGJAC; ↑ EAC; ↑ EGJAC</td>
</tr>
<tr>
<td>Chen et al. (2009) [58]</td>
<td>China</td>
<td>Hospital-based case-control study</td>
<td>41 EGJAC; 205 PC</td>
<td>Fresh V + F, rice</td>
<td>↓ EGJAC</td>
</tr>
<tr>
<td>Carman et al. (2009) [38]</td>
<td>USA</td>
<td>Prospective cohort study</td>
<td>382 EAC; 320 EGJAC; 500,000 PC</td>
<td>α-tocopherol γ-tocopherol Supplemental vitamin E</td>
<td>/EAC;/EGJAC; NS EGJAC; /EGJAC</td>
</tr>
</tbody>
</table>

EGJAC: esophagogastric junction cancer; PC: population controls; EAC: esophageal adenocarcinoma; V + F: vegetables and fruit; ↓: decreased risk; ↑: increased risk; NS: not significant; /: not correlated.
The role of diet in BE, EAC and EGJAC

In an US case-control study, the association between total meat intake, in particular red meat, and increased risk of EAC was described, while higher intake of meat, particularly poultry, and high-fat dairy was associated with increased risk of EGJAC [57].

Several studies have also observed a greater risk of EAC with high dietary intake of fat [3,31,33], while the correlation has not been noticed with EGJAC [3] or only a non-significant increase has been described [60].

In another study the increased risk of EAC and EGJAC with high intake of fat and red meat diminished and was not statistically significant after adjusting for fiber intake [55].

Discussion

With the increased incidence of EAC and EGJAC over the last decades, identification of modifiable risk factors, such as diet, is an attractive approach to primary prevention of these tumors. Currently, however, the data regarding specific dietary components and the risk of BE, EAC or EGJAC are limited and inconsistent. In our review of the literature, a consistent positive association was found between consumption of meat and high-fat meals and EAC and EGJAC. In contrast, some studies report an inverse association with increased intake of fruit, vegetables and antioxidants, but this association was not consistent across all studies reviewed. Few studies have examined the association between diet and BE.

Design factors may explain some of the differences in results from studies of fruit and vegetable consumption and cancer risk. Retrospective studies are subject to recall bias. In case-control studies, changes of dietary habits in cases could have occurred because of preclinical symptoms. For example, GERD can confound or modify a diet-cancer association, because of diet can influence the frequency of GERD. Finally, selection bias may exist where controls in the study are different from the underlying population of the cases [56]. In prospective studies the diet-cancer association may have been underestimated because of imprecise dietary measurements and limited variability of dietary intake within each cohort [59]. The role of other factors that can act in the carcinogenesis of EAC in BE patients, could be considered: the long-duration use of anti-reflux drugs in cases may influence the evolution of BE to cancer. Studies report a lower risk of developing dysplasia in BE patients receiving proton pump inhibitors (PPI) compared to patients not being treated with PPI or treated with histamine H2-receptor antagonists, which are less effective at controlling acid secretion [62,63]. In contrast, chronic PPI therapy leads to elevations in serum gastrin level which have been linked to increased proliferation in Barrett’s biopsy specimens in vitro [64]; in a recent a cross sectional study elevated serum gastrin has been found in BE patients taking PPIs with a history of high grade dysplasia (HGD) or EAC [65].

The potential mechanisms by which specific dietary factors might influence the carcinogenic pathway are unclear. In general terms, diet might influence the development of BE and EAC more directly such as acting on the integrity of esophageal mucosa or indirectly by affecting other known risk factors such as GERD or obesity [19,37,39,66]. Observational studies cannot completely adjust for potential confounding factors, therefore some of the associations may not be attributable to specific nutrients per se, but rather may reflect unmeasured dietary factors or may be correlated with other health behaviours such as tobacco use [3,34,67].

Dietary patterns high in fruits and vegetables or nutrients from plant sources tend to be inversely associated with meat and fat intake. Therefore, the beneficial effects might result from the fruit and vegetables themselves, from the fiber and antioxidants present in them, from a reduced intake of meat and fat or due to the overall reduction of obesity for people with diets high in fruits and vegetables [7,33,49,55].

High-fiber foods often have a higher content of anti-carcinogenic substances, such as antioxidants and photochemicals, but also may have a mechanical action removing or limiting the contact of carcinogens with the esophageal epithelium [68,69]. In addition, high-fiber diets may be, on average, lower in fat, meat and calories [55]. It has also been hypothesized that high-fiber intake may reduce the risk of hiatal hernia, erosive esophagitis and reflux symptoms [70,71].

Vegetables are a major source of ingested nitrate, which has carcinogetic proprieties that could nullify the positive impact of fiber [60]. Some studies suggest that nitrate derived from nitrogenous fertilizers found primarily in green leafy vegetables promotes carcinogenesis at the gastro-esophageal junction and, in subjects with reflux diseases, at distal esophagus. These are the anatomical sites where saliva encounters gastric juice and their interaction generates reactive nitrogen species, which are potentially mutagenic and carcinogenic [72,73]. A high-level of salivary nitrite is sustained over several hours after the ingestion of a high nitrate meal and the nitrite in the swallowed saliva is converted to nitric oxide (NO) when it reacts with ascorbic acid, the reduced form of vitamin C, at acid pH [72,74].

In patients with reflux disease, the highest luminal NO concentrations occurs within the esophagus potentially contributing to the formation of BE and EAC [75,76]. This effect could explain why a diet high in antioxidants and vitamin C may have a protective effect against cancer of distal stomach and not for the esophagogastric junction cancer [3,34,47,77].

A dose-response relationship between total caloric intake and the risk of EAC/EGJAC has been described as has a correlation between increased dietary intake of fat (in particular saturated and monounsaturated) and increased cancer risk [33,55]. The role of dietary fat on the onset of EAC, might be mediated by a high calories intake derived from carbohydrates. Thompson et al. reported a negative association between fat consumption and EAC, but in the multivariate model the percentage of calories from fat was positively associated with EAC after controlling for percentage of total energy from carbohydrates [78]. Other studies have also linked increased total caloric intake with an increased risk of BE and EAC and with obesity [79,80]. It is well-known that being overweight is a risk factor for both EAC and EGJAC, and the risk rises with an increasing body mass index (BMI: a measure of adiposity expressed in kg/m²) [81–83].

Central (abdominal) obesity rather than BMI alone may be the important risk factor for BE and EAC [79,80]. Abdominal obesity may predispose to GERD (increasing intra-abdominal pressure and altering gastrointestinal motility) and adipose
tissue may alter circulating levels of pro-proliferative and apoptosis inhibiting factors promoting esophageal carcinogenesis through GERD-independent mechanism [84–86].

Future research is needed to confirm the association of specific dietary components and clarify the mechanisms by which these components affect the risk of developing EAC and EGJAC. The success of potential interventions to modify diet depends on the proposed mechanism of risk reduction. For example, interventions to increase or decrease specific dietary elements may be different that interventions to reduce obesity. Future studies could advance our knowledge by emphasizing prospective designs to reduce recall bias by using validated dietary intake questionnaires and biological measures (e.g. serum levels) and by considering important confounders such as GERD symptoms, tobacco and alcohol use, biometrics (BMI, waist hip ratio), physical activity, and socioeconomic factors.

Conflict of interest statement

No potential conflict of interest relevant to this article was reported.

References

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disease? An evidence-based approach. AMA Arch Intern Med 2006;166(9):965—71 [review].


