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Dietary Factors and the Risks of Esophageal Adenocarcinoma and Barrett's Esophagus

Ai Kubo[1], **Douglas A. Corley**[1,2], **Christopher D. Jensen**[1], and **Rubinder Kaur**[1]

[1] Northern California Kaiser Permanente; Division of Research

[2] University of California, San Francisco; Department of Medicine and Comprehensive Cancer Center

Abstract

Incidence rates for esophageal adenocarcinoma have increased by over 500% during the past few decades without clear reasons. Gastroesophageal reflux disease (GERD), obesity, and smoking have been identified as risk factors, although the demographic distribution of these risk factors is not consistent with the demographic distribution of esophageal adenocarcinoma, which is substantially more common among whites and males than any other demographic groups. Numerous epidemiological studies have suggested associations between dietary factors and the risks of esophageal adenocarcinoma and its precursor, Barrett's esophagus, though a comprehensive review is lacking. The main aim of the present review is to consider the evidence linking dietary factors with the risks of esophageal adenocarcinoma, Barrett's esophagus, and the progression from Barrett's esophagus to esophageal adenocarcinoma. The existing epidemiological evidence is strongest for an inverse relationship between intake of vitamin C, β-carotene, fruits and vegetables, particularly raw fruits and vegetables and dark-green, leafy and cruciferous vegetables, carbohydrates, fiber and iron and the risk of esophageal adenocarcinoma and Barrett's esophagus. Patients at higher risk for Barrett's esophagus and esophageal adenocarcinoma may benefit from increasing their consumption of fruits and vegetables and reducing their intake of red meat and other processed food items. Further research is needed to evaluate the relationship between diet and the progression of Barrett's esophagus to esophageal adenocarcinoma. Evidence from cohort studies will help determine whether randomized chemoprevention trials are warranted for the primary prevention of Barrett's esophagus or its progression to cancer.

Introduction

The incidence of esophageal adenocarcinoma has increased by over 500% during the past three decades, and is continuing to increase rapidly.(1–4) Patients diagnosed with this condition have a very poor prognosis; the mean five-year survival for patients with advanced disease is less than 20%.(5) Barrett's esophagus is the only known precursor to esophageal adenocarcinoma and the strongest risk factor. Barrett's esophagus is a chronic active inflammatory condition in which the normal squamous epithelium of the esophagus is replaced by a metaplastic columnar epithelium, usually as a consequence of chronic gastroesophageal reflux disease (GERD).(6) Currently, there are limited therapeutic options to either prevent or treat esophageal adenocarcinoma. The high mortality and poor response

Corresponding author: Ai Kubo, Kaiser Permanente Division of Research, 2000 Broadway, Oakland, CA 94612, Tel: 510-891-3750, Fax: 510-891-3606, ai.kubo@kp.org.

to treating advanced-stage disease underscore the importance of implementing early interventions that address modifiable risk factors.(5)

There is a substantial racial and gender disparity in the incidence of esophageal adenocarcinoma and Barrett's esophagus: it is estimated that the incidence of esophageal adenocarcinoma is approximately six to eight fold greater in men than in women, and four times higher in whites than in African Americans.(7–15) In addition, there is geographical variation in the incidence of esophageal adenocarcinoma; a study using the U.S. Surveillance, Epidemiology, and End Results (SEER) reported the fastest rise in incidence occurred in the Seattle, WA area, while the slowest increase was reported in Utah.(4) Given the rapid increase in the overall incidence rate, and the variation in the change in rates among different geographic areas,(4,8) it is likely that lifestyle and/or environmental factors play important roles in the development of esophageal adenocarcinoma along with genetic factors. Although GERD, obesity, and smoking have been identified as modifiable risk factors of esophageal adenocarcinoma,(16) the demographic distribution of these risk factors do not appear to explain the rapid incidence changes among certain demographic groups: GERD is common among both genders and across race/ethnicities,(17) obesity and abdominal obesity are more prevalent among African Americans and other minority ethnic groups than among Caucasians,(17–18) and the general rate of smoking has declined substantially during the past several decades.(19–20)

A number of studies have identified diet as a risk factor or protective factor for esophageal adenocarcinoma and Barrett's esophagus, though a critical review of this literature is lacking. In a report from the World Cancer Research Fund and American Institute for Cancer Research (WCRF-AICR), intakes of fruits, non-starchy vegetables, β-carotene, and vitamins C and E were deemed "probably" protective against the risk of esophageal cancer, while the evidence linking fiber and folate intake to a lower disease risk was described as "limited."(21) 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.(21) Unfortunately, the report included studies of poor quality, and more importantly, it did not discriminate between different histological types of esophageal cancers (i.e., squamous cell carcinoma vs. adenocarcinoma) even though these two malignancies have substantially different risk factors and etiology.(16)

The main aim of the present review is to consider the evidence linking dietary factors with the risks of esophageal adenocarcinoma, Barrett's esophagus, and the progression from Barrett's esophagus to esophageal adenocarcinoma. Two authors (AK and RK) independently conducted literature searches of articles published prior to May 2010 (PubMed; National Library of Medicine, Bethesda, MD, USA) to find research articles that had: (1) evaluated human exposure to nutrients, foods, or beverages; (2) measured occurrence of esophageal adenocarcinoma, Barrett's esophagus, or progression of Barrett's esophagus to esophageal adenocarcinoma; (3) did not combine esophageal squamous cell carcinoma and adenocarcinoma as a single outcome; and (4) reported a relative risk, odds ratio, or other estimate of disease risk with confidence intervals or p-values. The inclusion criteria were not otherwise restricted by study size, language, or publication type. The lists of reviewed studies are presented in Table 1, 2, and 3: the tables are categorized by outcomes (e.g., esophageal adenocarcinoma (Table 1), Barrett's esophagus (Table 2), and progression from Barrett's esophagus to esophageal adenocarcinoma(Table 3)), by study design (e.g., cohort vs. case-control, when available), and country. The results are ordered by the strengths of the association (from protective to adverse) within each study/author, except for Table 3, which is arranged by the types of outcome measured.

Antioxidants and Other Vitamins/Minerals

Dietary antioxidants such as vitamin C, vitamin E, selenium, and carotenoids are believed to have the potential to reduce tissue and/or DNA damage by scavenging reactive oxygen species and enhancing apoptosis.(22) Thus, a lack of these nutrients may increase cancer risk through oxidative stress, DNA damage, and cell proliferation.(23) Previous studies have shown that markers of oxidative stress are increased in the presence of esophagitis and its complications, both in humans(24) and in animal models.(25) In addition, dietary antioxidants may help to modify the damaging effects of refluxed acid and bile in patients with GERD, thereby reducing the risk of developing Barrett's esophagus and its progression to esophageal adenocarcinoma. Animal studies have demonstrated that vitamin E or α-tocopherol inhibits the development of esophageal adenocarcinoma through its antioxidant properties, and inadequate selenium in the diet may promote carcinogenesis by enhancing oxidative stress.(26–27) Below are summaries of epidemiological evidence of the relationship between various dietary antioxidants and the risks of esophageal adenocarcinoma and Barrett's esophagus.

Vitamin C and β-Carotene

Of the eight studies that examined the association between β-carotene and vitamin C intake and the risk of esophageal adenocarcinoma, most studies have reported an inverse relationship (Table 1).(28–32) A recent meta-analysis that included these case-control studies reported significant inverse associations between vitamin C and β-carotene/vitamin A intake and disease risk [summary OR=0.49; 95% confidence interval [CI]=0.39–0.62; OR=0.46; 95% CI=0.36–0.59, comparing those in the 4^{th} vs. 1^{st} quartiles(Q) of intake, respectively].(33) A Swedish study stratified their results by the presence of reflux symptoms and reported a significant inverse association between β-carotene intake and esophageal adenocarcinoma only among individuals with reflux symptoms, suggesting the possibility that β-carotene may counteract the oxidative stress caused by chronic acid reflux.(30) Older case-control studies have reported no association between intakes of these micronutrients and esophageal adenocarcinoma.(34–36) However, two of these studies combined both esophageal adenocarcinoma and gastric cardia adenocarcinoma into a single outcome,(34,36) suggesting that dietary risk factors for these two malignancies may differ.

Only two studies have examined the effect of vitamin C or β-carotene intake on the risk of Barrett's esophagus (Table 2) or progression of Barrett's esophagus into cancer (Table 3). A population-based case-control study using a Kaiser Permanente Northern California population demonstrated that dietary intakes of vitamin C and β-carotene were inversely associated with the risk of Barrett's esophagus [OR=0.48; 95% CI=0.26–0.90; OR=0.56; 95% CI=0.32–0.99, Q4 vs. Q1, respectively].(37) This study also reported that dietary antioxidants were strongly inversely associated with GERD diagnosis, while there was no association between total (dietary and supplemental) intake and the risk of Barrett's esophagus. Lastly, a smaller study examining 48 Barrett's esophagus cases and 48 controls reported that cases with Barrett's esophagus had significantly lower plasma and tissue concentrations of vitamin C than controls (data not shown).(38)

Vitamin E

One cohort study and four case-control studies have evaluated the association between dietary vitamin E and the risk of esophageal adenocarcinoma, and one case-control study evaluated its effect on the risk of Barrett's esophagus. Contrary to the hypothesis from animal models, a large prospective cohort study (NIH-AARP) with 8 years of follow-up and 382 esophageal adenocarcinoma cases reported that vitamin E intake was adversely associated with the risk of esophageal adenocarcinoma in the fully adjusted continuous

model, [RR=1.05; 95% CI=1.00–1.11, per 1.17 mg/day], though in the categorical analysis the results were non-significant.(39) Most case-control studies of esophageal adenocarcinoma have reported no or borderline inverse associations with vitamin E intake,(29–30,36) while a German study of esophageal adenocarcinoma and a case-control study of Barrett's esophagus both reported strong inverse associations.(32)(37)

Selenium

Little is known about the effect of selenium intake on the risks of esophageal adenocarcinoma or Barrett's esophagus. One recent cohort study conducted in Netherlands evaluated the association between toenail selenium and the risk of esophageal adenocarcinoma, and reported no overall association. However, when stratified, inverse associations were found for women and non-smokers [RR=0.74–95%CI 0.64–0.86; RR=0.74–95%CI 0.64–0.86, respectively].(40) Two studies have evaluated the effect of selenium on Barrett's esophagus or progression from Barrett's esophagus into cancer. The Kaiser Permanente study showed borderline significant inverse association between self-reported selenium intake and the risk of Barrett's esophagus,(37) and a study from Seattle reported significant inverse associations between self-reported selenium intake and serum selenium concentrations and the progression of Barrett's esophagus into cancer. In this study, researchers examined 51 Barrett's esophagus patients and measured neoplastic progression using DNA content flow cytometry, where elevated proportions in the S and G2 phases are considered to predict progression to adenocarcinoma.(41) The study reported a significant inverse association between serum selenium levels and %S phase ($r = -0.34$), as well as for dietary selenium, particularly selenium from bread and grains, and the percentage of cells in the S and G_2 phase.(41) It is important to note that estimating selenium intake with a food frequency questionnaire (FFQ) has limited validity because the selenium content of foods varies substantially due to regional differences in soil selenium concentration. More studies are needed using more accurate measure of selenium such as toenail or serum levels.

Vitamin Supplement Use

Studies reporting the associations between vitamin supplement use and the risks of esophageal adenocarcinoma or Barrett's esophagus are mixed. Seven studies examined the association with esophageal adenocarcinoma, one studied Barrett's esophagus, and two evaluated the progression from Barrett's esophagus. For esophageal adenocarcinoma, most studies including a prospective study have reported either non-significant inverse associations or no association.(28–30,35,39,42) However, the study from Seattle reported that individuals who took 1 or more multivitamin pills/day during the past year had a significantly decreased risk of esophageal adenocarcinoma [HR=0.38; 95% CI=0.15–0.99] compared to those not taking multivitamins.(43) In addition, significant inverse associations were observed between supplemental vitamin C and E use and the risk of esophageal adenocarcinoma in this study [HR=0.25; 95% CI=0.11–0.58, ≥250 mg vs. none; HR=0.25; 95% CI=0.10–0.60, ≥180 mg vs. none, respectively].(43)

The only study to evaluate the association between supplement use and the risk of Barrett's esophagus reported that two or more years of vitamin supplement use (single or multivitamin antioxidants) was not associated with disease risk-in fact, there was a non-significant adverse association between some of the vitamin supplements and the risk of Barrett's esophagus.(37) On the other hand, a study from the Seattle Barrett's Esophagus Program reported a significant inverse association between supplement use and markers of progression of Barrett's esophagus into cancer as measured by DNA content flow cytometry and mucosal biopsies.(43) DNA content abnormalities such as increased 4N fractions, aneuploidy, and tetraploidy have been validated as being highly predictive of subsequent cancer development(44) and mechanistically related to the progression of Barrett's

esophagus to esophageal adenocarcinoma.(45–46) This study found that participants who took 1 or more multivitamin pills/day during the past year had a significantly decreased risk of tetraploidy [HR=0.19; 95% CI=0.08–0.47] compared to those not taking multivitamins.(43) However, another study from Seattle showed no association between multivitamin supplement use and %S or $\%G_2$ in DNA content flow cytometry.(41)

The mixed findings may partially be due to the inconsistent definition of supplement use (i.e., supplement type, duration, and dose). Also, given the latency period for progression to disease, long-term supplement use, rather than current use (or over the past year) may be a more appropriate way to define the relevant exposure. In observational studies, patients may start taking supplements after developing symptoms or receiving a diagnosis, leading to reverse causation. In addition, the methods for adjusting for other health-related factors varied among the studies. Supplement users tend to have healthier dietary habits, maintain healthy BMI, engage in more exercise, and have a higher socioeconomic status (SES).(47) Although many studies adjusted for at least some of these factors, there likely remains residual confounding from unmeasured factors. Randomized controlled trials will better answer the question as to whether vitamin supplementation may be useful as a chemoprevention strategy, especially among patients who have already developed Barrett's esophagus.

In sum, the current body of evidence is strongest for an inverse relationship between intake of vitamin C and β-carotene and the risks of Barrett's esophagus and esophageal adenocarcinoma, while the evidence regarding the effect on disease risk of vitamin E and selenium intake, as well as vitamin supplement use, remains inconclusive.

Fruits and Vegetables

Fruits and vegetables are sources of antioxidants, phytosterols, folic acid, and other substances which may inhibit carcinogenesis by various mechanisms including quenching free-radicals and blocking the formation of N-nitroso compounds.(48–50) Eleven studies have examined the association between fruits and vegetables and the risk of esophageal adenocarcinoma, and the majority of the case-control studies have reported significant inverse associations.(31,35,42,51–55) In fact, one U.S. study estimated that the population attributable risk, defined as the proportion of disease in the population attributable to a given risk factor, associated with low fruit and vegetable consumption was 15.3% [95% CI=5.8%–34.6%].(53) Similarly, a Swedish study estimated that about 20% of esophageal adenocarcinoma was attributed to low consumption (<3 servings/day) of fruits and vegetables.(56)

However, two large cohort studies reported no association between total intake of fruits and vegetables and the risk of esophageal adenocarcinoma.(57–58) In the NIH-AARP Diet and Health study that included 5 years of follow-up (2,193,751 person-years) and 213 esophageal adenocarcinoma cases, higher intake of fruits and vegetables was not associated with risk of esophageal adenocarcinoma [HR=0.99; 95% CI=0.61–1.61, Q5 vs. Q1].(57) Similarly, the European Prospective Study of Cancer and Nutrition (EPIC) with fewer cases (n=65) reported no associations with intake of fruits or vegetables [fruit: HR=0.94; 95% CI=0.49–1.80; vegetables: HR=0.71; 95% CI=0.34–1.48; 3^{rd} vs. 1^{st} tertile (T)].(58)

The beneficial effect of vegetables may be specific to certain botanical groups or types of vegetables. Dark green and cruciferous vegetables contain high levels of isothiocyanates and indole-3-carbinol which are thought to protect against the development of cancer.(59) Some epidemiological studies support this hypothesis. A recent study reported an inverse association between the intake of anthocyanidin, a flavonoid found commonly in raw vegetables, and the risk of esophageal adenocarcinoma among white males.(60) In case-

control studies that have evaluated intake of specific types of vegetables, stronger inverse associations were reported between esophageal adenocarcinoma and the intake of dark green, leafy green, or raw vegetables.(35–36,51,54) In addition, the NIH-AARP cohort study demonstrated that spinach intake was significantly associated with reduced esophageal adenocarcinoma risk [HR=0.66; 95% CI=0.46–0.95] and a borderline significant inverse association was found for cruciferous vegetables such as cabbage and broccoli [HR=0.69; 95% CI=0.48–1.00].(57) Similarly, the EPIC cohort study reported a borderline significant inverse association between leafy vegetables (excluding cabbage) and the risk of esophageal adenocarcinoma [OR=0.35; 95% CI=0.12–1.04; T3 vs. T1].(58)

Three population-based case-control studies have evaluated the associations between the intake of fruits and vegetables and the risk of Barrett's esophagus, and all have reported significant inverse associations.(37,52,61) A study from Ireland reported a 40% reduction in risk among those with >34 portions of fruits and vegetables per week, compared to those with <20 portions per week, though adjustment for GERD attenuated the association.(52) Similarly, a study from Kaiser Permanente reported a significant inverse association when the fruit and vegetable intake of Barrett's esophagus cases were compared to that of population controls. However, when cases were compared to GERD controls, the association was no longer significant,(37) suggesting that among GERD patients, intake of fruits and vegetables did not modify the risk. No cohort studies evaluated the association between fruits and vegetables and the risk of Barrett's esophagus.

Given the potential protective effect of fruit and vegetable intake, a randomized intervention trial was conducted to evaluate whether short-term dietary modification affects the progression of Barrett's esophagus into cancer.(62) In this trial, 87 patients were randomized to an intensive, low-fat, high-fruit and vegetable diet plus weight loss group or to a control group, and biopsies were obtained at baseline, and 18 and 36 months after the intervention. Ki67/DNA content flow cytometry was used to assess % Ki67-positive proliferating diploid G(1) cells, % total Ki67-positive proliferating cells, presence of aneuploidy, and presence of >6% of cells in the 4N (G(2)/tetraploid) fraction of the cell cycle, all of which are markers of cellular proliferation in Barrett's esophagus.(44,62) The intervention was effective at increasing fruit and vegetable consumption and promoting weight loss ($p<0.01$), though no significant effect on any biomarker of cellular proliferation was observed. Another Seattle study reported no association between fruit and vegetable intake and DNA content flow cytometry in Barrett's esophagus patients.(41) Thus, short term dietary modification does not appear to be effective in the progression to esophageal adenocarcinoma among patients with Barrett's esophagus. However, given the long latency period for disease progression, longer periods of intervention may be required.

Which components of fruits and vegetables are etiologically relevant and at what points in the carcinogenesis process of esophageal adenocarcinoma their intake may have an impact remains unclear. There are numerous known and unknown compounds in fruits and vegetables, and it is impossible to isolate their effects. One study evaluated whether other nutrients confound the observed strong inverse association between fruits and vegetables and Barrett's esophagus: adjustment for obesity, total energy, intakes of folic acid, total fat, saturated fat, trans fat, cholesterol, meat, isoflavones or fiber made no difference in the effect estimates, suggesting that a diet rich in fruits and vegetables is not simply a surrogate for other dietary factors.(63) However, residual confounding remains a possibility in observational studies.

In addition, the presence of GERD symptoms may influence health-related behaviors among Barrett's esophagus and esophageal adenocarcinoma patients. The presence of GERD is one of the strongest risk factors for both Barrett's esophagus and esophageal adenocarcinoma,

(16) and GERD patients are commonly advised to reduce their consumption of citrus or other acidic fruits and vegetables.(64) Thus, reverse causation may bias observational studies, even prospective cohort studies, since patients often experience GERD for many years prior to their cancer diagnosis. Indeed, studies that have adjusted for GERD symptoms have reported partial attenuation in the inverse association.(37,52) However, this also suggests the possibility that at least some of the effect of fruit and vegetable intake on disease risk is independent of GERD.

In sum, the current evidence suggests that fruits and vegetables, particularly raw fruits and vegetables, dark-green leafy vegetables, and cruciferous vegetables, may reduce the risk of Barrett's esophagus and esophageal adenocarcinoma. The current evidence also suggests that if there is a protective effect, it may take place early in the carcinogenesis process, given the strong inverse association between the intake of fruits and vegetables and Barrett's esophagus, and the lack of association with the progression of Barrett's esophagus into cancer. Evidence from cohort studies will help elucidate the relationships between the intake of fruits and vegetables and the risk of Barrett's esophagus.

Carbohydrate

A recent ecological study reported a correlation between the rise in carbohydrate consumption in the United States and the increase in the incidence of esophageal adenocarcinoma.(65) Chronic insulin resistance, hyperglycemia, and hyperinsulinemia have been implicated as potential risk factors for cancers of the breast, prostate, lung, and colon. Since both high-carbohydrate and high-glycemic index diets have been linked as possible contributors to these risk factors, carbohydrate intake has also been hypothesized to affect the risk of esophageal adenocarcinoma.(66–69) Insulin resistance and altered levels of insulin-like growth factor (IGF)-related compounds also have been reported to influence the healing of esophageal mucosal injury and esophageal cell apoptosis.(70–74) However, only limited epidemiological evidence is available on the relationships between carbohydrate intake and the risks of esophageal adenocarcinoma and Barrett's esophagus.

Six studies have examined the association between carbohydrate intake and the risk of esophageal adenocarcinoma and one study evaluated the association with Barrett's esophagus. Case-control studies have reported an inverse association between total carbohydrate intake and the risk of esophageal adenocarcinoma,(28–29,75) though not in all.(31,35–36) The FINBAR study conducted in Ireland included cases with reflux esophagitis, esophageal adenocarcinoma, and long-segment Barrett's esophagus, and reported that intakes of total carbohydrate, starch, and total sugar were associated with significantly lower risks of esophageal adenocarcinoma, but not with Barrett's esophagus.(75) On the other hand, glycemic index was positively associated with the risk of esophageal adenocarcinoma [OR=1.41; 95% CI=1.05–1.89, per 10 unit/day increment]. In addition, total carbohydrate and total sugar intake were inversely associated with the risk of reflux esophagitis, a risk factor for Barrett's esophagus [OR=0.67; 95% CI=0.42–1.04, per 50g/day increment in total carbohydrate; OR=0.54; 95%CI= 0.35–0.82, per 50g/day increment in total sugar, respectively], though total carbohydrate was of borderline significance. On the other hand, starch intake was positively associated with risk of reflux esophagitis [OR=2.25; 95% CI=1.15–4.41, per 50g/day increment in starch].

How carbohydrate intake might affect the etiology of esophageal adenocarcinoma remains unclear. It is possible that a high carbohydrate intake is a proxy for a higher intake of whole grains or fruits and vegetables that are rich in other bioactive micronutrients,(28,75) a lower intake of fat or animal products, or other suggested risk factors for esophageal adenocarcinoma discussed below.

Fiber

Nine studies have examined the association between fiber and esophageal adenocarcinoma. Most case-control studies of esophageal adenocarcinoma have reported strong, significant inverse associations between fiber intake and disease risk.(28–29,31,35,75–76) Earlier, smaller case-control studies also reported inverse associations between fiber and esophageal adenocarcinoma, although some combined both gastric cardia and esophageal adenocarcinoma into one outcome.(31,36) However, one of these studies reported a significant adverse association between total fiber and esophageal adenocarcinoma,(34)and a Swedish study also reported a borderline adverse association for intake of fiber from fruits and esophageal adenocarcinoma.(77)

Only two studies have evaluated the association between fiber intake and the risk of Barrett's esophagus. In the FINBAR study, the risk of Barrett's esophagus was significantly reduced in those in the highest versus the lowest tertile of fiber intake [OR=0.44; 95% CI=0.25–0.80], and the inverse association persisted even after controlling for fat, protein, starch, and sugar intake.(75) Similarly, a Kaiser Permanente study reported that total fiber intake was inversely related to Barrett's esophagus, though when stratified by fiber source, only fiber from fruits and vegetables (but not grains or beans) was associated with lower disease risk, raising the possibility that other food elements in fruits and vegetables may confound the association.(78)

There are a few potential mechanisms through which fiber intake might affect the etiology of Barrett's esophagus or esophageal adenocarcinoma. A recent study demonstrated that inositol hexaphosphate, a naturally occurring polyphosphorylated carbohydrate found in food sources high in fiber, inhibited the cell growth rate of Barrett's-associated esophageal adenocarcinoma cells in vitro by reducing cellular proliferation and promoting apoptosis.(79) In addition, a diet rich in fiber is associated with lower plasma levels of biomarkers of systemic inflammation such as tumor necrosis factor-alpha (TNF-α) receptor-2 and interleukin-6, potentially affecting the carcinogenesis process.(80) Also, fiber itself may absorb carcinogens from food items that pass through the digestive tract,(35) or reduce the risk of Barrett's esophagus by decreasing the risk of hiatal hernia.(81) However, similar to carbohydrate intake, the possibility that a high-fiber diet is a proxy for a diet rich in fruits and vegetables or micronutrients that are protective against these diseases cannot be ruled out. In sum, although the mechanisms remain unclear, current evidence suggests a strong inverse association between dietary fiber and the risk of esophageal adenocarcinoma. More studies are needed to evaluate the relationship between fiber intake and the risk of Barrett's esophagus, and results from cohort studies will help shed light on the association with esophageal adenocarcinoma.

Folate (Folic Acid)

Another nutrient of interest in fruits and vegetables, particularly green-leafy vegetables, is folate. Previous studies have linked folate intake and genetic polymorphisms in 5,10-methylenetetrahydrofolate reductase (MTHFR), a central enzyme in folate metabolism, with colorectal cancer.(82–83) Certain folate-metabolizing enzyme genotypes are associated with an increased risk of gastric cardia adenocarcinoma and esophageal squamous cell carcinoma.(84–85) Also, folate deficiency has been hypothesized to increase the risk of cancer via mediation by p53 tumor suppressor gene,(86) or by decreasing intracellular S-adenosylmethionine (SAM) which inhibits cytosine methylation in DNA, activating proto-oncogenes, inducing malignant transformations, causing DNA precursor imbalances, misincorporating uracil into DNA, and promoting chromosome breakage.(87) A recent small study evaluating the effect of dietary folate and vitamin B6 on p53 mutations in

esophageal adenocarcinoma reported that dietary intake was not associated with p53 mutations, p53 mutations at CpG sites, and p53 protein overexpression.(86)

Four studies have examined the association between folate and the risk of esophageal adenocarcinoma; all reported inverse associations, though some were of borderline significance.(28–29,35–36) A recent meta-analysis including these studies reported that individuals in the highest folate intake category were at half the risk of developing esophageal adenocarcinoma compared to those in the lowest category [summary OR=0.50; 95% CI=0.39–0.65].(84) No studies have evaluated the association between folate and Barrett's esophagus, progression from Barrett's esophagus into cancer, or the role of functional polymorphisms in genes encoding folate-metabolizing enzymes on the risk of esophageal adenocarcinoma or Barrett's esophagus.

It is important to note that alcohol (a folate antagonist), smoking (which impairs folate status), and other methyl-related nutrients (e.g., vitamin B6, vitamin B12, and methionine) impact the folate metabolic pathway, and may interact with folate and *MTHFR* polymorphisms to affect cancer risk.(88) In the studies of gastric cardia adenocarcinoma, strong effect modification has been observed between the MTHFR C677T polymorphism and alcohol drinking.(84) However, no studies to date have evaluated the interaction of dietary factors (i.e., alcohol and methyl-related nutrients) and folate-related genetic polymorphisms in relation to esophageal adenocarcinoma. In sum, there is evidence that dietary folate may reduce the risk of esophageal adenocarcinoma. Studies are needed to evaluate its effect on Barrett's esophagus, progression from Barrett's esophagus into cancer, and its interaction with potential effect modifiers including genetic polymorphism and alcohol consumption.

Meat, Heterocyclic Amines, and nitrate/nitrite

Meat intake has been linked to several cancers, including colorectal, breast and, prostate cancers.(89–90) Eight studies have examined the association between meat intake and the risk of esophageal adenocarcinoma, and one has studied the association with Barrett's esophagus. The results are mixed. In the EPIC prospective cohort study that involved a mean follow-up of 6.5 years and 65 newly-diagnosed cases of esophageal adenocarcinoma, a positive association was observed for processed meat [HR=3.54; 95% CI=1.57–7.99, T3 vs. T1] while the result for total meat intake was not significant [HR=1.79; 95% CI=0.86–3.75, T3 vs. T1]. (91) In a multicenter, population-based case-control study, total meat intake was associated with an increased risk of esophageal adenocarcinoma [OR=1.43; 95% CI=1.11–1.83, per serving/day], with red meat most strongly related to disease risk [OR=2.49; 95% CI=1.39–4.46, per serving/day].(51) In the same study population, animal protein intake was associated with an increased risk of esophageal adenocarcinoma, while vegetable protein intake was inversely related to risk.(29) However, a few case-control studies have reported no link between total or red meat intake and the risk of esophageal adenocarcinoma.(35–36,54) Also, a recent study of Barrett's esophagus reported that total meat intake was inversely related to long-segment Barrett's esophagus, [OR=0.25; 95% CI=0.09–0.72],(78) although this study did not stratify the results by type of meat. With regard to poultry intake, some studies have reported significant inverse associations with esophageal adenocarcinoma,(51,91) while others have reported borderline significant or positive associations.(28,36)

The inconsistency in results may at least partially be due to a combination of factors such as the type of meat, nutrient content (e.g., fat, protein, iron), nitrite/nitrate content, and/or meat preparation methods (e.g., cooking or preserving methods). Meats cooked at high temperatures (i.e., frying and grilling) and for a long duration contain heterocyclic amines

(HCAs) and polycyclic aromatic hydrocarbons (PAHs), potent mutagens that have been shown to induce tumors in animal models.(89) Total HCA intake was positively associated with the risk of upper aerodigestive tract cancers in a study conducted in Uruguay.(92) However, existing studies of esophageal adenocarcinoma and Barrett's esophagus have shown no association with cooking method/barbecued meat or well-cooked meat.(78,93–94) In addition, processed meat is a major source of nitrites and nitrosamines and a recent systematic review of epidemiological studies suggested an association between processed meat and the risk of esophageal cancers.(95) N-nitroso compounds (NNCs) are strong animal carcinogens and have been shown to cause cancers of the nasal cavity, esophagus, and stomach in several animal models,(96–98) and are considered "probably" carcinogenic to humans.(48) Although few studies have examined the relationship between intake of nitrite or nitrate and risk of esophageal adenocarcinoma, the US multicenter study reported a borderline significant positive association for dietary nitrite intake [OR=1.17; 95% CI=1.00–1.36],(29) and another study reported a non-significant positive association between dietary nitrite from animal sources and the risk of esophageal adenocarcinoma.(99) In addition, this study found a significant interaction between vitamin C and nitrite intakes: those with low vitamin C and high nitrite intake were at significantly higher risk of developing esophageal adenocarcinoma compared to those with high vitamin C and low nitrite intake [OR=2.72; 95% CI=1.73–4.27].(29) In the same study population, however, meat with high-nitrite was not associated with disease risk.(51) No study has evaluated the association between nitrite/nitrate and the risk of Barrett's esophagus or progression. Since pesticide on fruits and vegetables is another major source of nitrate, better understanding of the effects of nitrate/nitrate on the risk of esophageal adenocarcinoma or Barrett's esophagus has a significant public health implication before encouraging high risk individuals to consume large amount of fruits and vegetables.

In sum, evidence from cohort studies suggests an adverse association between meat intake and the risk of esophageal adenocarcinoma, particularly for red meat and processed meat. Further research is needed to evaluate types of meat and the risk of Barrett's esophagus, and the role of nitrite and nitrate, HCAs and PAHs in the etiology of esophageal adenocarcinoma and Barrett's esophagus.

Fat

Given the established relationships between obesity and the risk of Barrett's esophagus and esophageal adenocarcinoma,(16) a diet rich in fat is a suspected risk factor for these outcomes. Animal studies have reported an adverse effect of fat intake (total or animal) on Barrett's esophagus.(100–101) Among the seven case-control studies that evaluated the association between fat intake and the risk of esophageal adenocarcinoma, four reported an increased risk among individuals with high total fat intake compared to those in the lowest category of fat intake,(28–29,34,36) but three reported no association.(31,35,102) The only case-control study that evaluated the effect of fat on the risk of Barrett's esophagus found no association for total fat.(78) Lastly, modification of the diet by lowering fat and increasing fruit and vegetable consumption had no effect on the progression of Barrett's esophagus as measured by DNA content flow cytometry.(62)

The discrepancy in findings between studies may come from lack of specification of fat or fatty acid types. For instance, trans fats and saturated fats have been found to influence systemic inflammation such as TNF-α receptors 1 and 2.(103) A previous study reported that the epithelial expression of TNF-α increases with progression along the metaplasia-dysplasia-carcinoma sequence, suggesting an important role of TNF-α in the carcinogenesis process from Barrett's esophagus into esophageal adenocarcinoma.(104)

On the other hand, polyunsaturated fatty acids and omega-3 fatty acids, mainly found in plants and fish, may decrease the risk of esophageal adenocarcinoma. Omega-3 fatty acids have been found to reduce Cox-2 protein concentrations in Barrett's tissues in a small randomized study.(105) Upregulation of Cox-2 has been shown to occur in both Barrett's esophagus and esophageal adenocarcinoma.(106) Also, in vitro studies have demonstrated that Cox-2 can reduce the rate of apoptosis.(107) Corroborating the findings of these laboratory studies, a few epidemiological studies of esophageal adenocarcinoma and Barrett's esophagus have reported an inverse association between disease risk and either fish intake or a dietary pattern rich in fish.(28,36,108–109) These findings underscore the importance of differentiating the types or sources of fats and fatty acids when studying diet-disease relationships. Differentiation may help in making more targeted dietary recommendations, rather than, for example, suggesting a reduction in total fat intake, which risks limiting the intake of potentially-beneficial types of fats or fatty acids. Only a few epidemiological studies to date have evaluated different types of fatty acids.

One study found an adverse association between saturated fat or cholesterol intake and the risk of esophageal adenocarcinoma,(29) and a study of Barrett's esophagus reported an adverse association with trans-fat and saturated fat intake when examined continuously (data not shown), while omega-3 fatty acids were inversely related to the risk of Barrett's esophagus.(78) However, the overall data are inconclusive as other studies have found no association with saturated fat or cholesterol intake,(31,35) and no other studies have evaluated the effects of omega-3 fatty acids or trans fat intake. More studies, especially cohort studies, are needed to better understand the relationships between various types of fat and the risks of esophageal adenocarcinoma and Barrett's esophagus.

Carbonated Soft Drinks

Carbonated soft drinks have been suggested as a risk factor for esophageal adenocarcinoma because they are acidic and may increase reflux by reducing esophageal sphincter pressure,(110) though there has been little scientific evidence to support an association. Among the three studies that evaluated the association between carbonated soft drink consumption and the risk of esophageal adenocarcinoma, two large case-control studies in Sweden and Australia have reported no relationship.(111–112) In fact, a US multicenter study reported a strong inverse relationship between carbonated soft drink intake and esophageal adenocarcinoma [OR=0.47; 95% CI=0.29–0.76].(113) Therefore, the current data show no evidence that soft drink consumption increases the risk of esophageal adenocarcinoma, and no studies have evaluated its relationship with Barrett's esophagus or progression of Barrett's esophagus into cancer.

Iron

In animal models, iron supplementation before reflux-induced esophageal injury substantially increased the risk of esophageal metaplasia and esophageal adenocarcinoma, and the cells in these models demonstrated oxidative damage.(26,114) In addition, the effect of iron on esophageal adenocarcinoma etiology has been hypothesized because males are at higher risk for esophageal adenocarcinoma and Barrett's esophagus, and they typically have higher iron saturation levels compared to females.(115–117)

However, the epidemiological evidence related to iron and risk of esophageal adenocarcinoma or Barrett's esophagus is not consistent with the hypothesis that iron overload is a risk factor. In fact, three of the population-based case-control studies that evaluated this association suggested inverse associations,(29,35–36) and the only study of Barrett's esophagus also reported that levels of dietary iron and serum iron stores (ferritin and transferrin saturation) were lower among cases.(118) In sum, there is currently no

evidence that dietary iron intake or iron store are adversely associated with the risk of esophageal adenocarcinoma or Barrett's esophagus. On the contrary, the evidence suggests inverse association with these outcomes.

Dietary Patterns

Dietary factors are often strongly correlated and it is difficult to isolate the effect of a single factor. Individuals who differ in the consumption of one dietary component tend to differ in intake of other components. For instance, an individual with a high fiber intake may also have a high intake of fruits, vegetables, and carbohydrates, and consume a diet lower in meat and fat. This issue of correlated variables in diet-related epidemiologic studies makes it difficult to pinpoint the dietary component most likely to influence disease etiology. Compared with the conventional analytical approach that focuses on individual dietary factors, studying dietary patterns more effectively captures the complexity of dietary habits. By identifying the most common dietary patterns in a population, researchers can evaluate the overall effects of nutrients and food items consumed in combination. In addition, dietary pattern analysis is potentially useful in formulating dietary recommendations because it may be easier for patients to understand and incorporate recommendations for dietary patterns rather than increase or decrease their intake of a particular nutrient.(119)

Two studies have examined the association between dietary pattern and the risk of esophageal adenocarcinoma and one has reported on the association with Barrett's esophagus. A Swedish study reported that a "healthy" dietary pattern characterized by a high intake of vegetables, fruits, fish, and poultry was associated with lower risk of esophageal adenocarcinoma, and that a Western-style diet rich in processed meat, red meat, sweets, and fast foods was associated with an increased risk of esophageal adenocarcinoma, though the results were not statistically significant.(109) Another study reported that a high-meat dietary pattern had a borderline significant positive relationship with esophageal adenocarcinoma risk [OR=3.6; 95% CI=0.96–13.2].(54) A case-control study of Barrett's esophagus also reported a significant inverse association between disease risk and a dietary pattern rich in fruits, vegetables, and non-fried fish, along with a suggestive adverse association for a Western-style dietary pattern characterized by a higher intake of fast food and meat.(108)

Conclusions

The existing epidemiological evidence is strongest for an inverse relationship between intake of vitamin C, β-carotene, fruits and vegetables, particularly raw fruits and vegetables and dark-green, leafy and cruciferous vegetables, carbohydrates, fiber and iron and the risk of esophageal adenocarcinoma, and to a lesser degree, Barrett's esophagus. There is limited evidence that folate is inversely related and red meat and processed meat are positively related to the risk of esophageal adenocarcinoma. The current evidence does not support the hypothesis that carbonated beverages are associated with higher risk of esophageal adenocarcinoma, and the data are inconclusive about vitamin E, selenium, vitamin supplement intake, various fatty acids, nitrite/nitrate, and heterocyclic amine. The finding of diet-disease relationships for both Barrett's esophagus and esophageal adenocarcinoma suggests these dietary factors may act early in the carcinogenic pathway, rather than by decreasing the likelihood of Barrett's esophagus transforming into esophageal adenocarcinoma. Diet could, for example, alter the risk of gastroesophageal reflux itself or, among persons with reflux-induced damage, change their risk of getting Barrett's esophagus. Patients at higher risk for Barrett's esophagus and esophageal adenocarcinoma may benefit from adhering to an overall healthy dietary pattern by increasing their consumption of fresh fruits and vegetables and reducing their intake of red meat and other

processed food items. Gaps in this body of research include studies evaluating the impact of diet on the progression from Barrett's esophagus to esophageal adenocarcinoma, and on the influence of diet, particularly micronutrients, on the risk of Barrett's esophagus. Further evidence from cohort studies will help determine whether randomized chemoprevention trials would be warranted.

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Table 1

Studies on dietary factors and esophageal adenocarcinoma

Study name/Country	Author	Year	Study Design	N or PY	Type of food/nutrients	Comparison groups	OR/HR*	95%CI or p-value
Cohort studies								
NIH AARP USA	Freedman(57)	2007	Pop Cohort	2+mil PY 213 EA	Chenopodiaceae (spinach)	3rd vs 1st Tertile	0.66	0.46–0.95
					Cruciferous	3rd vs 1st Tertile	0.69	0.48–1.00
					Total Vegetables	5th vs. 1st Quintile	0.92	0.57–1.50
					Total FV	5th vs. 1st Quintile	0.99	0.61–1.61
					Total Fruits	5th vs. 1st Quintile	1.04	0.64–1.69
	Carman(39)	2009		3.5mil PY 382 EA	Dietary α-toco	4th vs. 1st Q	1.27	0.94–1.72
					Vitamin E suppl.	4th vs. 1st Q	0.91	0.56–1.48
EPIC Europe	Gonzalez(58)	2006	Pop Cohort	3+ mil PY 65 EA	Leafy Vegetables	3rd vs. 1st Tertile	0.35	0.12–1.04
					Total Vegetables	3rd vs. 1st Tertile	0.71	0.34–1.48
					Citrus	3rd vs. 1st Tertile	0.73	0.39–1.37
					Total Fruits	3rd vs. 1st Tertile	0.94	0.49–1.80
	Gonzalez(91)	2006			Red meat	3rd vs. 1st Tertile	1.67	0.75–3.72
					Total meat	3rd vs. 1st Tertile	1.79	0.86–3.75
					Poultry	3rd vs. 1st Tertile	1.93	0.99–3.76
					Processed	3rd vs. 1st Tertile	3.54	1.57–7.99
Netherland	Stevens(40)		Pop Cohort	120,852 Persons	Selenium (toenail)	Per unit increase	1.05	0.95–1.15
Case-Control Studies: USA								
US	Mayne(113)	2006	Pop CC	282 EA	Fiber	4th vs 1st Q	0.28	0.19–0.40
multicenter	Mayne(29)	2001		687 Cont	carbohydrate	4th vs 1st Q	0.34	0.20–0.58
					Protein (from Vegetables)	4th vs 1st Q	0.39	0.27–0.58
					Vitamin C	4th vs 1st Q	0.45	0.33–0.61
					Carbonated soda	4th vs 1st Q	0.47	0.29–0.76
					Vitamin A	4th vs 1st Q	0.47	0.34–0.66
					Folate	4th vs 1st Q	0.48	0.36–0.66

Study name/Country	Author	Year	Study Design	N or PY	Type of food/nutrients	Comparison groups	OR/HR*	95%CI or p-value
					Vitamin E	4th vs 1st Q	0.73	0.54–1.00
					Iron	4th vs 1st Q	0.79	0.57–1.09
					Polyunsaturated	4th vs 1st Q	0.86	0.59–1.24
					Nitrite	4th vs 1st Q	1.02	0.80–1.30
					multivitamin	Any vs. none	1.07	0.76–1.51
					Cholesterol	4th vs 1st Q	1.74	1.36–2.23
					Protein (Animal)	4th vs 1st Q	1.79	1.33–2.41
					Total Fat	4th vs 1st Q	2.18	1.27–3.76
					Saturated Fat	4th vs 1st Q	2.34	1.55–3.54
	Navarro Silvera(51)	2008			Dark Green	Per serving/day	0.52	0.32–0.86
					Cruciferous	Per serving/day	0.56	0.31–1.03
					Deep Yellow	Per serving/day	0.58	0.35–0.96
					Raw	Per serving/day	0.75	0.61–0.93
					Vegetables	Per serving/day	0.85	0.75–0.96
					Fruits	Per serving/day	0.85	0.75–0.96
					Grain	Per serving/day	1.05	0.89–1.23
					High Nitrite Meat	Per serving/day	1.34	0.84–2.15
					High fat Dairy	Per serving/day	1.34	1.09–1.63
					Fish	Per serving/day	1.39	0.61–3.19
					Meat	Per serving/day	1.43	1.11–1.83
					Poultry	Per serving/day	1.65	0.97–2.82
					Red meat	Per serving/day	2.49	1.39–4.46
Nebraska USA	Chen(54)	2002	Pop CC	124 EA 449 Cont	*Food types*			
					Fish	Q4 vs. Q1	0.14	0.04–0.48
					Dairy Products	Q4 vs. Q1	0.43	0.18–0.98
					Vegetables	Q4 vs. Q1	0.45	0.2–1.00
					Poultry	Q4 vs. Q1	0.47	0.17–1.30
					Citrus Fruits	Q4 vs. Q1	0.48	0.2–1.10
					Red Meat	Q4 vs. Q1	1.40	0.61–3.20
					Total Meat	Q4 vs. Q1	1.60	0.61–4.10

Study name/Country	Author	Year	Study Design	N or PY	Type of food/nutrients	Comparison groups	OR/HR*	95%CI or p-value
					Processed Meat	Q4 vs. Q1	1.70	0.71–3.90
					Dietary patterns			
					High dessert	Vs. healthy	1.6	0.39–6.90
					High Milk	Vs. healthy	2.5	0.64–9.80
					High white bread	Vs. healthy	2.6	0.77–8.70
					High salty snacks	Vs. healthy	2.9	0.85–9.90
					High meat	Vs. healthy	3.6	0.96–13.2
	Chen(28)				carbohydrate	Q4 vs. Q1	0.4	0.20–0.90
					Vitamin A	Q4 vs. Q1	0.5	0.30–1.00
					Folate	Q4 vs. Q1	0.5	0.30–1.00
					Fiber	Q4 vs. Q1	0.5	0.30–0.90
					Vitamin C	Q4 vs. Q1	0.6	0.30–1.00
	Ward(99)	2008	Pop CC	84 EA 324 cont	Dietary nitrite fm animal source	8.3+ vs.<3.8mg/d nitrate + nitrite	2.2	0.90–5.70
					Diet nitrite from plant sources	0.67+ vs. <0.36mg/d nitrite	1	0.40–2.40
					Diet nitrate from plant source	>38.8 vs. <16.9mg/d nitrate-nitrogen	0.8	0.30–1.80
	Ward(94)			143 EA 502 cont	Meat cooking methods/Types			
					Barbecue/grilled	Vs. baked/boiled	1.5	0.5–4.8
					Well done	Vs. rare/medium rare	1.5	0.6–5.6
					Processed meat	8+/wk vs. <4/wk	1.7	0.9–3.3
					Red meat	19+/week vs. <8	2.0	1.0–4.0
NY	Kabat(34)	1993	Hosp CC	121CA+EA 4544 cont	Vitamin C	4th vs. 1st Q	0.9	0.5–1.70
					Vitamin A from plant	4th vs. 1st Q	1	0.5–2.00
					Vitamin A from animal	4th vs. 1st Q	2.4	1.3–4.60
					Total Fat	4th vs. 1st Q	2.9	1.5–5.60
					Fiber	4th vs. 1st Q	3.2	1.5–7.00
US White men	Brown(35)	1995	Pop CC White Male only	174 EA 750 Cont	Cruciferous vegetables	4th vs. 1st Q	0.3	p<0.001
					Raw Fruits	4th vs. 1st Q	0.4	0.05
					Raw vegetables	4th vs. 1st Q	0.4	0.1

Study name/Country	Author	Year	Study Design	N or PY	Type of food/nutrients	Comparison groups	OR/HR*	95%CI or p-value
					Fiber	4th vs. 1st Q	0.4	0.004
					Iron	4th vs. 1st Q	0.5	ns
					Vegetables	4th vs. 1st Q	0.6	ns
					Dark Green vegetables	4th vs. 1st Q	0.6	ns
					Dark Yellow vegetables	4th vs. 1st Q	0.6	0.1
					Folate	4th vs. 1st Q	0.6	ns
					Total meat	4th vs. 1st Q	0.7	ns
					Processed Meats	4th vs. 1st Q	0.7	ns
					Fruits	4th vs. 1st Q	0.7	ns
					Red Meat	4th vs. 1st Q	0.8	ns
					Vitamin A	4th vs. 1st Q	0.8	ns
					Poultry, Fish	4th vs. 1st Q	0.9	ns
					Vitamin C	4th vs. 1st Q	0.9	ns
					Total fat	4th vs. 1st Q	1.1	ns
					Dairy products	4th vs. 1st Q	1.1	ns
					Grains, Cereal	4th vs. 1st Q	1.1	ns
					Saturated fat	4th vs. 1st Q	1.7	ns
					Carbohydrate	4th vs. 1st Q	1.9	ns
	Bobe(60)	2009		161 EA 678 Cont	Anthocyanidins	4th vs. 1st Q	0.47	0.24–0.91
NYC	Zhang(36)	1997	Hosp CC	95 EA/CA 200 Cont	Non Citrus	4th vs. 1st Q	0.6	0.4–0.90
					Dark green veg	4th vs. 1st Q	0.6	0.3–0.98
					Fiber	4th vs. 1st Q	0.6	0.4–0.90
					Iron	4th vs. 1st Q	0.6	0.3–0.90
					Poultry, Fish	4th vs. 1st Q	0.7	0.5–1.00
					Raw Fruits	4th vs. 1st Q	0.7	0.5–1.00
					Vitamin E	4th vs. 1st Q	0.7	0.5–1.10
					Folate	4th vs. 1st Q	0.7	0.4–1.00
					Fruits	4th vs. 1st Q	0.8	0.5–1.20
					Protein	4th vs. 1st Q	0.8	0.6–1.20
					carbohydrate	4th vs. 1st Q	0.8	0.5–1.10

Study name/Country	Author	Year	Study Design	N or PY	Type of food/nutrients	Comparison groups	OR/HR*	95%CI or p-value
					Vitamin A	4th vs. 1st Q	0.8	0.5–1.20
					Total meat & fish	4th vs. 1st Q	0.9	0.7–1.30
					Citrus	4th vs. 1st Q	0.9	0.6–1.30
					Vegetables	4th vs. 1st Q	0.9	0.6–1.30
					Vitamin C	4th vs. 1st Q	1.0	0.8–1.50
					Dairy	4th vs. 1st Q	1.1	0.–1.60
					Red Meat	4th vs. 1st Q	1.1	0.8–1.60
					Processed Meats	4th vs. 1st Q	1.3	0.9–1.80
					Fat	4th vs. 1st Q	1.6	1.1–2.40
Seattle	Dong(43)	2008	Cohort	339 BE	Vitamin C	≥ 250mg vs. none	0.25	0.11–0.58
					Vitamin E	≥ 180mg vs. none	0.25	0.10–0.60
					Selenium	≥ 50μg vs. none	0.27	0.03–2.21
					Any multivitamin	1+/day vs. no users	0.38	0.15–0.99
					β-Carotene	≥ 1800μg vs. none	0.99	0.34–2.94
European Case-control studies								
Sweden	Lagergren(111)	2006	Pop CC	185 EA	Carbonated soda	>6/week vs. none	0.8	0.6–1.90
	Bahmanyar(19)	2006		820 Cont	Healthy Dietary pattern	High vs. Low	0.8	0.5–1.30
					Western Dietary pattern	High vs. Low	1.6	0.9–3.10
	Terry(77)	2001			Cereal fiber	7th vs. 1st Q	0.7	0.4–1.2
					Total fiber	4th vs. 1st Q	0.8	0.5–1.3
					Vegetable fiber	6th vs. 1st Q	0.8	0.5–1.5
					Fruits fiber	5th vs. 1st Q	1.7	1.0–2.9
	Terry(56)	2001			FV		EF=32%	6–51%
	Terry(93)	2003			Heterocyclic amines			NS
	Terry(30)	2000			β-Carotene	4th vs. 1st Q	0.5	0.3–0.80
					Vitamin C	4th vs. 1st Q	0.7	0.4–1.10
					α-tocopherol	4th vs. 1st Q	0.9	0.5–1.60

Study name/Country	Author	Year	Study Design	N or PY	Type of food/nutrients	Comparison groups	OR/HR*	95%CI or p-value
	Terry(98)	2000			Portion size	4th vs. 1st Q	0.6	0.4–1.10
					Total fat	118–160g vs. 23–95g/day	0.8	0.5–1.40
Greece	Tzonou(31)	1996	Hosp CC	56 EA 200 cont	Vitamin C	Per quintile	0.54	0.40–0.72
					Vitamin A	Per quintile	0.62	0.46–0.83
					Vegetables	Per quintile	0.62	0.48–0.80
					Crude Fiber	Per quintile	0.74	0.55–0.99
					Fruits	Per quintile	0.84	0.65–1.08
					Protein	Per quintile	0.84	0.56–1.27
					carbohydrate	Per quintile	0.84	0.59–1.19
					Saturated Fat	Per quintile	0.99	0.68–1.44
					Cholesterol	Per quintile	1.06	0.75–1.51
					Meats and Fish	Per quintile	1.07	0.83–1.37
					Monounsaturated	Per quintile	1.07	0.72–1.60
					Total Fat	Per quintile	1.18	0.76–1.85
					Polyunsaturated	Per quintile	1.35	0.94–1.94
FINBAR Ireland	Anderson(52)	2007	Pop CC	227 EA 260 Cont	Fruits	>20 vs. <5/wk	0.47	0.28–0.8
					FV	>34 vs. <20/wk	0.67	0.41–1.12
					Vegetable	>17 vs. <12/wk	1.38	0.84–2.28
	Mulholand (75)	2008		224 EA 256 Cont	carbohydrate	340 vs. <265 g/d	0.39	0.16–0.94
					Total Sugar	≥ 162.9 vs. <115.9g/d	0.43	0.19–0.94
					Englyst Fiber	≥ 17.7 vs. <13.7 g/d	0.84	0.47–1.53
					Starch	≥ 175.0 vs. <136.0g/d	0.84	0.40–1.76
					Glycemic Load	≥ 135 vs. <102 g/d	1.14	0.55–2.33
					Glycemic index	≥ 44 vs. <36 g/d	1.50	0.84–2.76
Germany	Bollschweiler(32)	2002	Hosp CC Male only	47 EA 50 Cont	Vitamin E	>13 vs. <13mg	0.13	0.09–0.54
					Vitamin C	>100 vs. ≤100mg/d	0.33	0.11–0.92
UK	Cheng(42)	2000	Pop CC Females Only	74 EA 74 Control	Fruits	>25 vs. <12/wk	0.08	0.01–0.49
					Salad Vegetables	> 17 vs. 0–6/wk	0.31†	0.10–0.92

Study name/Country	Author	Year	Study Design	N or PY	Type of food/nutrients	Comparison groups	OR/HR*	95%CI or p-value
					Fruit Juice	>1/d vs. <1/d	0.40†	0.14–1.11
					Vegetables	> 25 vs. <15/wk	0.58†	0.22–1.55
Australian case-control studies								
Australia	Ibiebele(112)	2008	PopCC	294 EA	Carbonated drink	≥ 1/d vs. none	0.94	0.53–1.66
				1484 Cont				

Abbreviations: N, sample size; PY, person-years; OR, odds ratio; HR, hazard ratio; CI, confidence interval; pop: population-based; mil, million; FV, fruits and vegetables; EA, esophageal adenocarcinoma; Q, quartile; suppl, supplement; CC, case-control; cont, control; NS, non-significant; EF, etiological fraction; hosp, hospital-based; wk, week.

*Adjusted HR/OR for the highest dietary intake compared with the lowest dietary intake, unless otherwise noted.

†Unadjusted OR

Table 2

Studies on dietary factors and Barrett's esophagus (all population-based case-control studies)

Study name	Author	Year	N	Type of food/nutrients	Comparison groups*	OR†	95%CI
USA population-based case-control studies							
Kaiser Permanente USA	Kubo(37)	2008	296 BE 309 Cont	*Dietary*			
				Vitamin E	19 vs. 5.4mig/d	0.25	0.11–0.59
				Vitamin C	184 vs. 43mg/d	0.48	0.26–0.90
				β-Carotene	6.8 vs. 1.8 mg/d	0.56	0.32–0.99
				Selenium	133 vs. 46mig/d	0.58	0.26–1.30
				Supplement use			
				Fruits/vegetables	8.3 vs. 2.0/d	0.27	0.15–0.50
				Selenium	73 vs. 52mig/d	1.13	0.93–1.37
				Vitamin E	170 vs. 25mig/d	1.20	0.63–2.28
				Vitamin C	610 vs.150mg/d	1.26	0.68–2.33
				β-Carotene	3.5 vs. 1.3mig/d	1.77	0.94–3.34
	Kubo(108	2008		Dietary pattern			
				Healthy Diet	4^{th} vs. 1^{st} Q	0.35	0.20–0.64
				Western Diet	4^{th} vs. 1^{st} Q	1.39	0.66–2.93
	Kubo(78)	2009		Total Fiber	29.7 vs. 8.6g/d	0.34	0.15–0.76
				Omega-3	3.02 vs. 0.83g/d	0.46	0.22–0.97
				Meat	3.3 vs. 0.9 servings/d	0.46	0.21–1.01
				Fiber from FV	13.2 vs. 3.2g/d	0.47	0.25–0.88
				Protein	103.4 vs. 37.4g/d	0.47	0.19–1.12
				Total Fat	131.4 vs. 39.6g/d	0.49	0.20–1.20
				Polyunsaturated	34.7 vs. 9.3g/d	0.49	0.22–1.11
				Monounsaturated	50.5 vs. 14.3 g/d	0.54	0.23–1.28
				Fiber from Beans	5.99 vs. 0.74g/d	0.69	0.36–1.33
				Cholesterol	370 vs. 51mg/d	0.70	0.34–1.44
				Fiber from Grains	12.3 vs. 3.1g/d	0.73	0.36–1.45
				Barbecued Food	1+/wk vs.<1/m	0.84	0.53–1.35

Study name	Author	Year	N	Type of food/nutrients	Comparison groups*	OR†	95%CI
				Dairy	2.2 vs. 0.2 servings/d	0.95	0.56–1.60
				Saturated fat	36.1 vs. 10.6g/d	1.05	0.47–2.34
				Meat doneness	Well done vs. rare	1.3	0.62–2.72
				Trans-fat	8.9 vs. 2.2g/d	1.54	0.76–3.10
	Corley(118)	2008	319 BE 313 Cont	*Iron intake*			
				Dietary Intake	21.9 vs. 7.7mg	0.37	0.17–0.80
				Total Intake	36.6 vs. 9.30mg	0.84	0.49–1.45
				Iron store			
				Ferritin	291 vs. 38ng/ml	0.24	0.14–0.40
				Iron Saturation	30 vs. 13%	0.66	0.41–1.04
Seattle USA	Thompson(61)	2009	170 BE 182 cont	Vegetables	≥ 1.24 vs. <0.67/1000 Kcal/d	0.33	0.17–0.63
				FV	≥ 2.31 vs. <1.24/1000 Kcal/d	0.39	0.21–0.75
				Fruits	>1.00 vs. <0.44/1000 Kcal/d	0.76	0.42–1.36
European population-based case-control studies							
FINBAR Ireland	Anderson(52)	2007	224 BE 260 Cont	Fruits	>20 vs. <5/wk	0.57	0.35–0.94
				FV	>34 vs. <20/wk	0.61	0.38–0.98
				Vegetables	>17 vs. < 12/wk	0.72	0.44–1.15
Mulholand(75)		2008	220 BE 256 Cont	Englyst Fiber	≥ 17.7 vs. <13.7g/d	0.44	0.25–0.80
				Glycemic Load	≥ 135.6 vs. <102.3	0.79	0.39–1.58
				Glycemic index	≥ 44.2 vs. <36.5	0.93	0.53–1.64
				Carbohydrate	≥ 340.3 vs. <264.87g/d	1.02	0.44–2.35
				Starch	≥ 175.0 vs. <136.0g/d	1.08	0.52–2.22
				Total Sugar	≥ 162.9 vs. <115.9g/d	1.12	0.53–2.37

N, sample size; OR, odds ratio; CI, confidence interval; pop: population-based; CC, case-control; BE, Barrett's esophagus; cont, control; d, day; FV, fruits and vegetables; Q, quartile.

*Percentile or median values unless exact cutoff points are indicated. Units are serving or portion unless specified.

†Adjusted OR for the highest dietary intake compared with the lowest dietary intake, unless otherwise noted.

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Table 3

Studies examining dietary factors and progression from Barrett's esophagus into esophageal adenocarcinoma

Study name	Author	Year	Study Design	N	Type of food/nutrients	Measures of progression	OR or r*	95%CI
US studies								
Seattle cohort USA	Dong(43)	2008	Cohort	339 BE	Any multivitamin pills/d vs. none	Tetraploidy	0.19	0.08–0.47
					Any multivitamin	Aneuploidy	0.62	0.22–1.72
					VitC ≥250mg vs. none	Tetraploidy	0.47	0.22–1.03
					VitC ≥250mg vs. none	Aneuploidy	0.52	0.21–1.30
					VitE ≥180mg vs. none	Tetraploidy	0.30	0.14–0.64
					VitE ≥180mg vs. none	Aneuploidy	0.58	0.22–1.52
					β-Caro ≥1800μg vs. none	Tetraploidy	0.61	0.22–1.74
					β-Caro ≥1800μg vs. none	Aneuploidy	0.25	0.03–2.12
					Selenium ≥50μg vs. none	Tetraploidy	0.26	0.07–0.99
					Selenium ≥50μg vs. none	Aneuploidy	0.22	0.03–1.85
	Kristal(62)	2005	Intervention	87 BE	Low fat, high FV diet vs. control	%ki67-positive proliferating diploid G1 cells		NS
						% total Ki67-positive proliferating cells		NS
						Presence aneuploidy		NS
						Presence of .6% of cells in the 4N fraction of cell cycle		NS
	Moe(41)	2000	Cross-Sectional	51 BE	Serum Selenium	% of cells in the S phases	r=−0.34	p <0.05
					Dietary Selenium	% of cells in the S phase	r=−0.32	p <0.05
						% of cells in the G2 phase	r=−0.31	p <0.01
European studies								
UK	Mehta(105)	2008	RCT	52 BE	Dietary supplement of n-3 fatty acid eicosapentaenoic acid (EPA) 1.5g/d for 6 months	Tissue levels of COX-2		Significant decline ($p < 0.05$) among EPA group vs. controls
						Prostaglandin E2		NS
						Leukotriene B4		NS

Abbreviations: N, sample size; OR, odds ratio; r, correlation; CI, confidence interval; BE, Barrett's esophagus; EA, esophageal adenocarcinoma; vit C, vitamin C; vitE, vitamin E; β-Caro, β-Carotene; FV, fruits and vegetables; RCT, randomized clinical trial; COX-2, cyclooxygenase-2.

*Adjusted OR for the highest dietary intake compared with the lowest dietary intake, unless otherwise noted.