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Dietary factors and the risks of oesophageal adenocarcinoma and Barrett's oesophagus

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Incidence rates for oesophageal adenocarcinoma have increased by over 500 % during the past few decades without clear reasons. Gastro-oesophageal reflux disease, 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 oesophageal 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 oesophageal adenocarcinoma and its precursor, Barrett's oesophagus, 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 oesophageal adenocarcinoma, Barrett's oesophagus, and the progression from Barrett's oesophagus to oesophageal 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, fibre and Fe and the risk of oesophageal adenocarcinoma and Barrett's oesophagus. Patients at higher risk for Barrett's oesophagus and oesophageal 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 oesophagus to oesophageal adenocarcinoma. Evidence from cohort studies will help determine whether randomised chemoprevention trials are warranted for the primary prevention of Barrett's oesophagus or its progression to cancer.

Barrett's oesophagus: Oesophageal adenocarcinoma: Dietary factors

Introduction

The incidence of oesophageal 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 5-year survival for patients with advanced disease is less than 20 %[5]. Barrett's oesophagus is the only known precursor to oesophageal adenocarcinoma and the strongest risk factor. Barrett's oesophagus is a chronic active inflammatory condition in which the normal squamous epithelium of the oesophagus is replaced by a metaplastic columnar epithelium, usually as a consequence of chronic gastro-oesophageal reflux disease (GERD)[6]. Currently, there are limited therapeutic options to either prevent or treat oesophageal adenocarcinoma. The high mortality and poor response to treating advanced-stage disease underscore the importance of implementing early interventions that address modifiable risk factors[5].

There is a substantial racial and sex disparity in the incidence of oesophageal adenocarcinoma and Barrett's oesophagus: it is estimated that the incidence of oesophageal 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 oesophageal adenocarcinoma; a study using the US Surveillance, Epidemiology, and End Results (SEER) reported that the fastest rise in incidence occurred in the Seattle area (WA, USA), while the slowest increase was reported in Utah (USA)[4]. Given the rapid increase in the

Abbreviations: EPIC, European Prospective Study of Cancer and Nutrition; GERD, gastro-oesophageal reflux disease; HR, hazard ratio; MTHFR, 5,10-methylenetetrahydrofolate reductase; NIH-AARP, National Institutes of Health–American Association of Retired Persons; Q, quartile; RR, relative risk; T, tertile.

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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 oesophageal adenocarcinoma along with genetic factors. Although GERD, obesity and smoking have been identified as modifiable risk factors of oesophageal adenocarcinoma[16], the demographic distribution of these risk factors does not appear to explain the rapid incidence changes among certain demographic groups: GERD is common among both sexes 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 oesophageal adenocarcinoma and Barrett's oesophagus, though a critical review of this literature is lacking. In a report from the World Cancer Research Fund and American Institute for Cancer Research, intakes of fruits, non-starchy vegetables, β-carotene, and vitamins C and E were deemed 'probably' protective against the risk of oesophageal cancer, while the evidence linking fibre and folate intake to a lower disease risk was described as 'limited'[21]. The report also indicated that the 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 oesophageal cancer[21]. Unfortunately, the report included studies of poor quality, and, more importantly, it did not discriminate between different histological types of oesophageal cancers (i.e. squamous cell carcinoma *v.* adenocarcinoma) even though these two malignancies have substantially different risk factors and aetiology[16].

The main aim of the present review is to consider the evidence linking dietary factors with the risks of oesophageal adenocarcinoma, Barrett's oesophagus, and the progression from Barrett's oesophagus to oesophageal adenocarcinoma. Two authors (A. K. and R. K.) independently conducted literature searches of articles published before 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 oesophageal adenocarcinoma, Barrett's oesophagus, or progression of Barrett's oesophagus to oesophageal adenocarcinoma; (3) did not combine oesophageal squamous cell carcinoma and adenocarcinoma as a single outcome; and (4) reported a relative risk (RR), OR, or other estimate of disease risk with CI 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 Tables 1–3: the tables are categorised by outcomes (for example, oesophageal adenocarcinoma (Table 1), Barrett's oesophagus (Table 2) and progression from Barrett's oesophagus to oesophageal adenocarcinoma (Table 3)), by study design (for example, cohort *v.* case–control, when available) and country. The results are ordered by the strengths of the association (from protective to adverse) within each study or 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, Se 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 oesophagitis 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 oesophagus and its progression to oesophageal adenocarcinoma. Animal studies have demonstrated that vitamin E or α-tocopherol inhibits the development of oesophageal adenocarcinoma through its antioxidant properties, and inadequate Se 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 oesophageal adenocarcinoma and Barrett's oesophagus.

Vitamin C and β-carotene

Of the eight studies that examined the association between β-carotene and vitamin C intake and the risk of oesophageal 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 % CI 0·39, 0·62; OR 0·46, 95 % CI 0·36, 0·59; comparing those in the 4th *v.* 1st 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 oesophageal 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 oesophageal adenocarcinoma[34–36]. However, two of these studies combined both oesophageal 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 oesophagus (Table 2) or progression of Barrett's oesophagus 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 oesophagus (OR 0·48, 95 % CI 0·26, 0·90; OR 0·56; 95 % CI 0·32, 0·99; Q4 *v.* 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 oesophagus. Lastly, a smaller study examining

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Table 1. Studies on dietary factors and oesophageal adenocarcinoma

Study name and country	First author	Year	Study design	Sample size (*n*) or PY	Type of food or nutrients	Comparison groups	OR or HR*	95% CI or *P*
Cohort studies								
NIH-AARP, USA	Freedman[57]	2007	Population-based cohort	2 + million PY	Chenopodiaceae (spinach)	3rd *v.* 1st tertile	0·66	0·46, 0·95
				213 EA	Cruciferous vegetables	3rd *v.* 1st tertile	0·69	0·48, 1·00
					Total vegetables	5th *v.* 1st quintile	0·92	0·57, 1·50
					Total fruit and vegetables	5th *v.* 1st quintile	0·99	0·61, 1·61
					Total fruits	5th *v.* 1st quintile	1·04	0·64, 1·69
	Carman[39]	2009		3·5 million PY	Dietary α-tocopherol	4th *v.* 1st Q	1·27	0·94, 1·72
				382 EA	Vitamin E supplements	4th *v.* 1st Q	0·91	0·56, 1·48
EPIC, Europe	Gonzalez[58]	2006	Population-based cohort	3 + million PY	Leafy vegetables	3rd *v.* 1st tertile	0·35	0·12, 1·04
				65 EA	Total vegetables	3rd *v.* 1st tertile	0·71	0·34, 1·48
					Citrus fruits	3rd *v.* 1st tertile	0·73	0·39, 1·37
					Total fruits	3rd *v.* 1st tertile	0·94	0·49, 1·80
	Gonzalez[91]	2006			Red meat	3rd *v.* 1st tertile	1·67	0·75, 3·72
					Total meat	3rd *v.* 1st tertile	1·79	0·86, 3·75
					Poultry	3rd *v.* 1st tertile	1·93	0·99, 3·76
					Processed meat	3rd *v.* 1st tertile	3·54	1·57, 7·99
The Netherlands Cohort Study, The Netherlands	Stevens[40]		Population-based cohort	120 852 individuals	Se (toenail)	Per unit increase	1·05	0·95, 1·15
Case–control studies: USA								
US multicentre	Mayne[113]	2006	Population-based case–control	282 EA	Fibre	4th *v.* 1st Q	0·28	0·19, 0·40
	Mayne[29]	2001		687 controls	Carbohydrate	4th *v.* 1st Q	0·34	0·20, 0·58
					Protein (from vegetables)	4th *v.* 1st Q	0·39	0·27, 0·58
					Vitamin C	4th *v.* 1st Q	0·45	0·33, 0·61
					Carbonated soda	4th *v.* 1st Q	0·47	0·29, 0·76
					Vitamin A	4th *v.* 1st Q	0·47	0·34, 0·66
					Folate	4th *v.* 1st Q	0·48	0·36, 0·66
					Vitamin E	4th *v.* 1st Q	0·73	0·54, 1·00
					Fe	4th *v.* 1st Q	0·79	0·57, 1·09
					Polyunsaturated fats	4th *v.* 1st Q	0·86	0·59, 1·24
					Nitrite	4th *v.* 1st Q	1·02	0·80, 1·30
					Multivitamins	Any *v.* none	1·07	0·76, 1·51
					Cholesterol	4th *v.* 1st Q	1·74	1·36, 2·23
					Protein (animal)	4th *v.* 1st Q	1·79	1·33, 2·41
					Total fat	4th *v.* 1st Q	2·18	1·27, 3·76
					Saturated fat	4th *v.* 1st Q	2·34	1·55, 3·54
	Navarro[51]	2008			Dark green vegetables	Per serving/d	0·52	0·32, 0·86
					Cruciferous vegetables	Per serving/d	0·56	0·31, 1·03
					Deep yellow vegetables	Per serving/d	0·58	0·35, 0·96
					Raw vegetables	Per serving/d	0·75	0·61, 0·93
					Vegetables	Per serving/d	0·85	0·75, 0·96
					Fruits	Per serving/d	0·85	0·75, 0·96
					Grain	Per serving/d	1·05	0·89, 1·23
					High-nitrite meat	Per serving/d	1·34	0·84, 2·15
					High-fat dairy	Per serving/d	1·34	1·09, 1·63

					Fish	Per serving/d	1·39	0·61, 3·19
					Meat	Per serving/d	1·43	1·11, 1·83
					Poultry	Per serving/d	1·65	0·97, 2·82
					Red meat	Per serving/d	2·49	1·39, 4·46
Nebraska, USA	Chen[54]	2002	Population-based case–control	124 EA	Food types			
				449 controls	Fish	Q4 *v.* Q1	0·14	0·04, 0·48
					Dairy products	Q4 *v.* Q1	0·43	0·18, 0·98
					Vegetables	Q4 *v.* Q1	0·45	0·2, 1·00
					Poultry	Q4 *v.* Q1	0·47	0·17, 1·30
					Citrus fruits	Q4 *v.* Q1	0·48	0·21, 1·10
					Red meat	Q4 *v.* Q1	1·40	0·61, 3·20
					Total meat	Q4 *v.* Q1	1·60	0·61, 4·10
					Processed meat	Q4 *v.* Q1	1·70	0·71, 3·90
					Dietary patterns			
					High desserts	*v.* Healthy	1·6	0·39, 6·90
					High milk	*v.* Healthy	2·5	0·64, 9·80
					High white bread	*v.* Healthy	2·6	0·77, 8·70
					High salty snacks	*v.* Healthy	2·9	0·85, 9·90
					High meat	*v.* Healthy	3·6	0·96, 13·2
	Chen[28]				Carbohydrate	Q4 *v.* Q1	0·4	0·20, 0·90
					Vitamin A	Q4 *v.* Q1	0·5	0·30, 1·00
					Folate	Q4 *v.* Q1	0·5	0·30, 1·00
					Fibre	Q4 *v.* Q1	0·5	0·30, 0·90
					Vitamin C	Q4 *v.* Q1	0·6	0·30, 1·00
	Ward[99]	2008	Population-based case–control	84 EA	Dietary nitrite from animal sources	8·3 + *v.* <3·8 mg/d nitrate + nitrite	2·2	0·90, 5·70
				324 controls				
					Diet nitrite from plant sources	0·67 + *v.* <0·36 mg/d nitrite	1	0·40, 2·40
					Diet nitrate from plant source	>38·8 *v.* <16·9 mg/d nitrate-nitrogen	0·8	0·30, 1·80
	Ward[94]			143 EA	Meat cooking methods/types			
				502 controls	Barbecue/grilled	*v.* baked/boiled	1·5	0·5, 4·8
					Well done	*v.* rare/medium rare	1·5	0·6, 5·6
					Processed meat	8 + *v.* <4 per week	1·7	0·9, 3·3
					Red meat	19 + *v.* <8 per week	2·0	1·0, 4·0
New York	Kabat[34]	1993	Hospital-based case–control	121 CA + EA	Vitamin C	4th *v.* 1st Q	0·9	0·5, 1·70
				4544 controls	Vitamin A from plants	4th *v.* 1st Q	1	0·5, 2·00
					Vitamin A from animals	4th *v.* 1st Q	2·4	1·3, 4·60
					Total fat	4th *v.* 1st Q	2·9	1·5, 5·60
					Fibre	4th *v.* 1st Q	3·2	1·5, 7·00
US white men	Brown[35]	1995	Population-based case–control	174 EA	Cruciferous vegetables	4th *v.* 1st Q	0·3	$P < 0·001$
			White males only	750 controls	Raw fruits	4th *v.* 1st Q	0·4	0·05
					Raw vegetables	4th *v.* 1st Q	0·4	0·1
					Fibre	4th *v.* 1st Q	0·4	0·004
					Fe	4th *v.* 1st Q	0·5	NS
					Vegetables	4th *v.* 1st Q	0·6	NS
					Dark green vegetables	4th *v.* 1st Q	0·6	NS
					Dark yellow vegetables	4th *v.* 1st Q	0·6	0·1
					Folate	4th *v.* 1st Q	0·6	NS
					Total meat	4th *v.* 1st Q	0·7	NS
					Processed meats	4th *v.* 1st Q	0·7	NS

Table 1. *Continued*

Study name and country	First author	Year	Study design	Sample size (*n*) or PY	Type of food or nutrients	Comparison groups	OR or HR*	95 % CI or *P*
					Fruits	4th *v.* 1st Q	0·7	NS
					Red meat	4th *v.* 1st Q	0·8	NS
					Vitamin A	4th *v.* 1st Q	0·8	NS
					Poultry, fish	4th *v.* 1st Q	0·9	NS
					Vitamin C	4th *v.* 1st Q	0·9	NS
					Total fat	4th *v.* 1st Q	1·1	NS
					Dairy products	4th *v.* 1st Q	1·1	NS
					Grains, cereal	4th *v.* 1st Q	1·1	NS
					Saturated fat	4th *v.* 1st Q	1·7	NS
					Carbohydrate	4th *v.* 1st Q	1·9	NS
	Bobe[60]	2009		161 EA 678 controls	Anthocyanidins	4th *v.* 1st Q	0·47	0·24, 0·91
New York City	Zhang[36]	1997	Hospital-based case–control	95 EA + CA	Non-citrus fruits	4th *v.* 1st Q	0·6	0·4, 0·90
				200 controls	Dark green vegetables	4th *v.* 1st Q	0·6	0·3, 0·98
					Fibre	4th *v.* 1st Q	0·6	0·4, 0·90
					Fe	4th *v.* 1st Q	0·6	0·3, 0·90
					Poultry, fish	4th *v.* 1st Q	0·7	0·5, 1·00
					Raw fruits	4th *v.* 1st Q	0·7	0·5, 1·00
					Vitamin E	4th *v.* 1st Q	0·7	0·5, 1·10
					Folate	4th *v.* 1st Q	0·7	0·4, 1·00
					Fruits	4th *v.* 1st Q	0·8	0·5, 1·20
					Protein	4th *v.* 1st Q	0·8	0·6, 1·20
					Carbohydrate	4th *v.* 1st Q	0·8	0·5, 1·10
					Vitamin A	4th *v.* 1st Q	0·8	0·5, 1·20
					Total meat and fish	4th *v.* 1st Q	0·9	0·7, 1·30
					Citrus fruits	4th *v.* 1st Q	0·9	0·6, 1·30
					Vegetables	4th *v.* 1st Q	0·9	0·6, 1·30
					Vitamin C	4th *v.* 1st Q	1·0	0·8, 1·50
					Dairy	4th *v.* 1st Q	1·1	0·8, 1·60
					Red meat	4th *v.* 1st Q	1·1	0·8, 1·60
					Processed meats	4th *v.* 1st Q	1·3	0·9, 1·80
					Fat	4th *v.* 1st Q	1·6	1·1, 2·40
Case–control studies: Europe								
Sweden	Lagergren[111]	2006	Population-based case–control	185 EA	Carbonated soda	>6/week *v.* none	0·8	0·6, 1·90
	Bahmanyar[19]	2006		820 controls	Healthy dietary pattern	High *v.* low	0·8	0·5, 1·30
					Western dietary pattern	High *v.* low	1·6	0·9, 3·10
	Terry[77]	2001			Cereal fibre	7th *v.* 1st Q	0·7	0·4, 1·2
					Total fibre	4th *v.* 1st Q	0·8	0·5, 1·3
					Vegetable fibre	6th *v.* 1st Q	0·8	0·5, 1·5
					Fruits fibre	5th *v.* 1st Q	1·7	1·0, 2·9
	Terry[56]	2001			Fruit and vegetables		EF = 32 %	6–51 %
	Terry[93]	2003			Heterocyclic amines			NS
	Terry[30]	2000			β-Carotene	4th *v.* 1st Q	0·5	0·3, 0·80
					Vitamin C	4th *v.* 1st Q	0·7	0·4, 1·10
					α-Tocopherol	4th *v.* 1st Q	0·9	0·5, 1·60
	Terry[98]	2000			Portion size	4th *v.* 1st Q	0·6	0·4, 1·10
					Total fat	118–160 g *v.* 23–95 g/d	0·8	0·5, 1·40
Greece	Tzonou[31]	1996	Hospital-based case–control	56 EA	Vitamin C	Per quintile	0·54	0·40, 0·72

				200 controls	Vitamin A	Per quintile	0·62	0·46, 0·83
					Vegetables	Per quintile	0·62	0·48, 0·80
					Crude fibre	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 fat	Per quintile	1·07	0·72, 1·60
					Total fat	Per quintile	1·18	0·76, 1·85
					Polyunsaturated fat	Per quintile	1·35	0·94, 1·94
FINBAR, Ireland	Anderson[52]	2007	Population-based case–control	227 EA	Fruits	>20 *v.* <5 per week	0·47	0·28, 0·8
				260 controls	Fruit and vegetables	>34 *v.* <20 per week	0·67	0·41, 1·12
					Vegetable	>17 *v.* <12 per week	1·38	0·84, 2·28
	Mulholland[75]	2008		224 EA	Carbohydrate	≥340 *v.* <265 g/d	0·39	0·16, 0·94
				256 controls	Total sugar	≥162·9 *v.* <115·9 g/d	0·43	0·19, 0·94
					Englyst fibre	≥17·7 *v.* <13·7 g/d	0·84	0·47, 1·53
					Starch	≥175·0 *v.* <136·0 g/d	0·84	0·40, 1·76
					Glycaemic load	≥135 *v.* <102 g/d	1·14	0·55, 2·33
					Glycaemic index	≥44 *v.* <36 g/d	1·50	0·84, 2·76
Germany	Bollschweiler[32]	2002	Hospital-based case–control	47 EA	Vitamin E	>13 *v.* <13 mg	0·13	0·09, 0·54
			Male only	50 controls	Vitamin C	>100 *v.* ≤ 100 mg/d	0·33	0·11, 0·92
UK	Cheng[42]	2000	Population-based case–control	74 EA	Fruits	>25 *v.* <12 per week	0·08	0·01, 0·49
			Females only	74 controls	Salad vegetables	>17 *v.* 0–6 per week	0·31†	0·10, 0·92
					Fruit juice	>1/d *v.* <1/d	0·40†	0·14, 1·11
					Vegetables	>25 *v.* <15 per week	0·58†	0·22, 1·55
Australian case–control studies								
Australia	Ibiebele[112]	2008	Population-based case–control	294 EA	Carbonated drinks	≥1/d *v.* none	0·94	0·53, 1·66
				1484 controls				

PY, person-years; HR, hazard ratio; NIH-AARP, National Institutes of Health–American Association of Retired Persons; EA, oesophageal adenocarcinoma; Q, quartile; EPIC, European Prospective Study of Cancer and Nutrition; CA, cardia adenocarcinoma; EF, aetiological fraction; FINBAR, Factors Influencing the Barrett's Adenocarcinoma Relationship.
* Adjusted HR or 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 oesophagus (BE) (all population-based case–control studies)

Study name	First author	Year	Sample size (*n*)	Type of food or nutrients	Comparison groups*	OR†	95 % CI
Population-based case–control studies: USA							
Kaiser Permanente, USA	Kubo[37]	2008	296 BE 309 controls	Dietary			
				Vitamin E	19 *v.* 5·4 μg/d	0·25	0·11, 0·59
				Vitamin C	184 *v.* 43 mg/d	0·48	0·26, 0·90
				β-Carotene	6·8 *v.* 1·8 mg/d	0·56	0·32, 0·99
				Se	133 *v.* 46 μg/d	0·58	0·26, 1·30
				Fruits/vegetables	8·3 *v.* 2·0/d	0·27	0·15, 0·50
				Supplement use			
				Se	73 *v.* 52 μg/d	1·13	0·93, 1·37
				Vitamin E	170 *v.* 25 μg/d	1·20	0·63, 2·28
				Vitamin C	610 *v.* 150 mg/d	1·26	0·68, 2·33
				β-Carotene	3·5 *v.* 1·3 μg/d	1·77	0·94, 3·34
	Kubo[108]	2008		Dietary pattern			
				Healthy diet	4th *v.* 1st quartile	0·35	0·20, 0·64
				Western diet	4th *v.* 1st quartile	1·39	0·66, 2·93
	Kubo[78]	2009		Total fibre	29·7 *v.* 8·6 g/d	0·34	0·15, 0·76
				n-3	3·02 *v.* 0·83 g/d	0·46	0·22, 0·97
				Meat	3·3 *v.* 0·9 servings/d	0·46	0·21, 1·01
				Fibre from fruit and vegetables	13·2 *v.* 3·2 g/d	0·47	0·25, 0·88
				Protein	103·4 *v.* 37·4 g/d	0·47	0·19, 1·12
				Total fat	131·4 *v.* 39·6 g/d	0·49	0·20, 1·20
				Polyunsaturated fat	34·7 *v.* 9·3 g/d	0·49	0·22, 1·11
				Monounsaturated fat	50·5 *v.* 14·3 g/d	0·54	0·23, 1·28
				Fibre from beans	5·99 *v.* 0·74 g/d	0·69	0·36, 1·33
				Cholesterol	370 *v.* 51 mg/d	0·70	0·34, 1·44
				Fibre from grains	12·3 *v.* 3·1 g/d	0·73	0·36, 1·45
				Barbecued food	1 + /week *v.* < 1/month	0·84	0·53, 1·35
				Dairy	2·2 *v.* 0·2 servings/d	0·95	0·56, 1·60
				Saturated fat	36·1 *v.* 10·6 g/d	1·05	0·47, 2·34
				Meat doneness	Well done *v.* rare	1·30	0·62, 2·72
				Trans-fat	8·9 *v.* 2·2 g/d	1·54	0·76, 3·10
	Corley[118]	2008	319 BE 313 controls	Fe intake			
				Dietary intake	21·9 *v.* 7·7 mg	0·37	0·17, 0·80
				Total intake	36·6 *v.* 9·30 mg	0·84	0·49, 1·45
				Fe stores			
				Ferritin	291 *v.* 38 ng/ml	0·24	0·14, 0·40
				Fe saturation	30 *v.* 13 %	0·66	0·41, 1·04
Seattle, USA	Thompson[61]	2009	170 BE 182 controls	Vegetables	≥1·24 *v.* < 0·67/1000 kcal/d‡	0·33	0·17, 0·63
				Fruit and vegetables	≥2·31 *v.* < 1·24/1000 kcal/d‡	0·39	0·21, 0·75
				Fruits	> 1·00 *v.* < 0·44/1000 kcal/d‡	0·76	0·42, 1·36
Population-based case–control studies: Europe							
FINBAR, Ireland	Anderson[52]	2007	224 BE 260 controls	Fruits	> 20 *v.* < 5 per week	0·57	0·35, 0·94
				Fruit and vegetables	> 34 *v.* < 20 per week	0·61	0·38, 0·98
				Vegetables	> 17 *v.* < 12 per week	0·72	0·44, 1·15
	Mulholland[75]	2008	220 BE 256 controla	Englyst fibre	≥17·7 *v.* < 13·7 g/d	0·44	0·25, 0·80
				Glycaemic load	≥135·6 *v.* < 102·3	0·79	0·39, 1·58
				Glycaemic index	≥44·2 *v.* < 36·5	0·93	0·53, 1·64
				Carbohydrate	≥340·3 *v.* < 264·87 g/d	1·02	0·44, 2·35
				Starch	≥175·0 *v.* < 136·0 g/d	1·08	0·52, 2·22
				Total sugar	≥162·9 *v.* < 115·9 g/d	1·12	0·53, 2·37

FINBAR, Factors Influencing the Barrett's Adenocarcinoma Relationship.

* Percentile or median values unless exact cut-off 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.

‡ 1000 kcal = 4184 kJ.

Table 3. Studies examining dietary factors and progression from Barrett's oesophagus (BE) into oesophageal adenocarcinoma

Study name	First author	Year	Study design	Sample size (*n*)	Type of food or nutrients	Measures of progression	OR or *r**	95 % CI
USA								
Seattle cohort (USA)	Dong[43]	2008	Cohort	339 BE	Any multivitamin pills/d *v.* none	Tetraploidy	0·19	0·08, 0·47
					Any multivitamin	Aneuploidy	0·62	0·22, 1·72
					Any multivitamin	EA	0·38	0·15, 0·99
					Vitamin C ≥ 250 mg *v.* none	Tetraploidy	0·47	0·22, 1·03
					Vitamin C ≥ 250 mg *v.* none	Aneuploidy	0·52	0·21, 1·30
					Vitamin C ≥ 250 mg *v.* none	EA	0·25	0·11, 0·58
					Vitamin E ≥ 180 mg *v.* none	Tetraploidy	0·30	0·14, 0·64
					Vitamin E ≥ 180 mg *v.* none	Aneuploidy	0·58	0·22, 1·52
					Vitamin E ≥ 180 mg *v.* none	EA	0·25	0·10, 0·60
					β-Carotene ≥ 1800 μg *v.* none	Tetraploidy	0·61	0·22, 1·74
					β-Carotene ≥ 1800 μg *v.* none	Aneuploidy	0·25	0·03, 2·12
					β-Carotene ≥ 1800 μg *v.* none	EA	0·99	0·34, 2·94
					Se ≥ 50 μg *v.* none	Tetraploidy	0·26	0·07, 0·99
					Se ≥ 50 μg *v.* none	Aneuploidy	0·22	0·03, 1·85
					Se ≥ 50 μg *v.* none	EA	0·27	0·03, 2·21
	Kristal[62]	2005	Intervention	87 BE	Low-fat, high-fruit and vegetable diet *v.* control	% Ki67-positive proliferating diploid G_1 cells		NS
						% Total Ki67-positive proliferating cells		NS
						Presence of aneuploidy		NS
						Presence of 0·6 % of cells in the 4N fraction of cell cycle		NS
	Moe[41]	2000	Cross-sectional	51 BE	Serum Se	% of cells in the S phases	r −0·34	$P < 0·05$
					Dietary Se	% of cells in the S phase	r −0·32	$P < 0·05$
						% of cells in the G_2 phase	r −0·31	$P < 0·01$
European								
UK	Mehta[105]	2008	RCT	52 BE	Dietary supplement of *n*-3 fatty acid EPA 1·5 g/d for 6 months	Tissue levels of COX-2		Significant decline ($P < 0·05$) among EPA group *v.* controls
						PGE_2		NS
						Leukotriene B4		NS

r, Correlation; EA, oesophageal adenocarcinoma; RCT, randomised clinical trial; COX-2, cyclo-oxygenase 2.
* Adjusted OR for the highest dietary intake compared with the lowest dietary intake, unless otherwise noted.

forty-eight Barrett's oesophagus cases and forty-eight controls reported that cases with Barrett's oesophagus 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 oesophageal adenocarcinoma, and one case–control study evaluated its effect on the risk of Barrett's oesophagus. Contrary to the hypothesis from animal models, a large prospective cohort study (National Institutes of Health–American Association of Retired Persons; NIH-AARP) with 8 years of follow-up and 382 oesophageal adenocarcinoma cases reported that vitamin E intake was adversely associated with the risk of oesophageal adenocarcinoma in the fully adjusted continuous model (RR 1·05; 95 % CI 1·00, 1·11; per 1·17 mg/d), though in the categorical analysis the results were non-significant[39]. Most case–control studies of oesophageal adenocarcinoma have reported no or borderline inverse associations with vitamin E intake[29,30,36], while a German study of oesophageal adenocarcinoma and a case–control study of Barrett's oesophagus both reported strong inverse associations[32,37].

Selenium

Little is known about the effect of Se intake on the risks of oesophageal adenocarcinoma or Barrett's oesophagus. One recent cohort study conducted in The Netherlands evaluated the association between toenail Se and the risk of oesophageal 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 Se on Barrett's oesophagus or progression from Barrett's oesophagus into cancer. The Kaiser Permanente study showed a borderline significant inverse association between self-reported Se intake and the risk of Barrett's oesophagus[37], and a study from Seattle reported significant inverse associations between self-reported Se intake and serum Se concentrations and the progression of Barrett's oesophagus into cancer. In this study, researchers examined fifty-one Barrett's oesophagus patients and measured neoplastic progression using DNA content flow cytometry, where elevated proportions in the S and G_2 phases are considered to predict progression to adenocarcinoma[41]. The study reported a significant inverse association between serum Se levels and percentage S phase (r −0·34), as well as for dietary Se, particularly Se from bread and grains, and the percentage of cells in the S and G_2 phase[41]. It is important to note that estimating Se intake with a FFQ has limited validity because the Se content of foods varies substantially due to regional differences in soil Se concentration. More studies are needed using more accurate measure of Se such as toenail or serum levels.

Vitamin supplement use

Studies reporting the associations between vitamin supplement use and the risks of oesophageal adenocarcinoma or Barrett's oesophagus are mixed. Of the studies, seven examined the association with oesophageal adenocarcinoma, one studied Barrett's oesophagus, and two evaluated the progression from Barrett's oesophagus. For oesophageal 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 one or more multivitamin pills per d during the previous year had a significantly decreased risk of oesophageal adenocarcinoma (hazard ratio (HR) 0·38; 95 % CI 0·15, 0·99) compared with those not taking multivitamins[43]. In addition, significant inverse associations were observed between supplemental vitamin C and E use and the risk of oesophageal adenocarcinoma in this study (HR 0·25, 95 % CI 0·11, 0·58, ≥ 250 mg *v.* none; HR 0·25, 95 % CI 0·10, 0·60, ≥ 180 mg *v.* none, respectively)[43].

The only study to evaluate the association between supplement use and the risk of Barrett's oesophagus reported that 2 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 oesophagus[37]. On the other hand, a study from the Seattle Barrett's Oesophagus Program reported a significant inverse association between supplement use and markers of progression of Barrett's oesophagus 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 oesophagus to oesophageal adenocarcinoma[45,46]. This study found that participants who took one or more multivitamin pills per d during the previous year had a significantly decreased risk of tetraploidy (HR 0·19; 95 % CI 0·08, 0·47) compared with those not taking multivitamins[43]. However, another study from Seattle showed no association between multivitamin supplement use and percentage S or percentage 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 previous 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 socio-economic status[47]. Although many studies adjusted for at least some of these factors, there probably remains residual confounding from unmeasured factors. Randomised controlled trials will better answer the question

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as to whether vitamin supplementation may be useful as a chemoprevention strategy, especially among patients who have already developed Barrett's oesophagus.

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 oesophagus and oesophageal adenocarcinoma, while the evidence regarding the effect on disease risk of vitamin E and Se 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 oesophageal adenocarcinoma, and the majority of the case–control studies have reported significant inverse associations[31,35,42,51–55]. In fact, one US 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 oesophageal adenocarcinoma was attributed to low consumption (less than three servings per d) of fruits and vegetables[56].

However, two large cohort studies reported no association between total intake of fruits and vegetables and the risk of oesophageal adenocarcinoma[57,58]. In the NIH-AARP Diet and Health study that included 5 years of follow-up (2 193 751 individual years) and 213 oesophageal adenocarcinoma cases, higher intake of fruits and vegetables was not associated with risk of oesophageal adenocarcinoma (HR 0·99; 95 % CI 0·61, 1·61; Q5 *v.* 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; 3rd *v.* 1st 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 oesophageal adenocarcinoma among white males[60]. In case–control studies that have evaluated the intake of specific types of vegetables, stronger inverse associations were reported between oesophageal 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 oesophageal 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 oesophageal adenocarcinoma (OR 0·35, 95 % CI 0·12, 1·04; T3 *v.* 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 oesophagus, and all have reported significant inverse associations[37,52,61]. A study from Ireland reported a 40 % reduction in risk among those with more than thirty-four portions of fruits and vegetables per week, compared with those with less than twenty 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 oesophagus cases was compared with that of population controls. However, when cases were compared with 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 oesophagus.

Given the potential protective effect of fruit and vegetable intake, a randomised intervention trial was conducted to evaluate whether short-term dietary modification affects the progression of Barrett's oesophagus into cancer[62]. In this trial, eighty-seven patients were randomised 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 at 18 and 36 months after the intervention. Ki67/DNA content flow cytometry was used to assess percentage Ki67-positive proliferating diploid G_1 cells, percentage 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 oesophagus[44,62]. The intervention was effective at increasing fruit and vegetable consumption and promoting weight loss ($P < 0{\cdot}01$), 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 oesophagus patients[41]. Thus, short-term dietary modification does not appear to be effective in the progression to oesophageal adenocarcinoma among patients with Barrett's oesophagus. However, given the long latency period for disease progression, longer periods of intervention may be required.

Which components of fruits and vegetables are aetiologically relevant and at what points in the carcinogenesis process of oesophageal adenocarcinoma their intake may have an impact remain 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 oesophagus: adjustment for obesity, total energy, intakes of folic acid, total fat, saturated fat, *trans*-fat, cholesterol, meat, isoflavones or fibre 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.

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In addition, the presence of GERD symptoms may influence health-related behaviours among Barrett's oesophagus and oesophageal adenocarcinoma patients. The presence of GERD is one of the strongest risk factors for both Barrett's oesophagus and oesophageal 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 before 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 oesophagus and oesophageal 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 oesophagus, and the lack of association with the progression of Barrett's oesophagus into cancer. Evidence from cohort studies will help elucidate the relationships between the intake of fruits and vegetables and the risk of Barrett's oesophagus.

Carbohydrate

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

Six studies have examined the association between carbohydrate intake and the risk of oesophageal adenocarcinoma and one study evaluated the association with Barrett's oesophagus. Case–control studies have reported an inverse association between total carbohydrate intake and the risk of oesophageal adenocarcinoma[28,29,75], though not in all[31,35,36]. The Factors Influencing the Barrett's Adenocarcinoma Relationship (FINBAR) study conducted in Ireland included cases with reflux oesophagitis, oesophageal adenocarcinoma and long-segment Barrett's oesophagus, and reported that intakes of total carbohydrate, starch and total sugar were associated with significantly lower risks of oesophageal adenocarcinoma, but not with Barrett's oesophagus[75]. On the other hand, glycaemic index was positively associated with the risk of oesophageal adenocarcinoma (OR 1·41; 95 % CI 1·05, 1·89; per 10 units/d increment). In addition, total carbohydrate intake and total sugar intake were inversely associated with the risk of reflux oesophagitis, a risk factor for Barrett's oesophagus (OR 0·67; 95 % CI 0·42, 1·04; per 50 g/d increment in total carbohydrate; OR 0·54; 95 % CI 0·35, 0·82; per 50 g/d 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 oesophagitis (OR 2·25; 95 % CI 1·15, 4·41; per 50 g/d increment in starch).

How carbohydrate intake might affect the aetiology of oesophageal 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 oesophageal adenocarcinoma discussed below.

Fibre

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

Only two studies have evaluated the association between fibre intake and the risk of Barrett's oesophagus. In the FINBAR study, the risk of Barrett's oesophagus was significantly reduced in those in the highest *v.* the lowest tertile of fibre 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 fibre intake was inversely related to Barrett's oesophagus, though when stratified by fibre source, only fibre 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 fibre intake might affect the aetiology of Barrett's oesophagus or oesophageal adenocarcinoma. A recent study demonstrated that inositol hexaphosphate, a naturally occurring polyphosphorylated carbohydrate found in food sources high in fibre, inhibited the cell growth rate of Barrett's-associated oesophageal adenocarcinoma cells *in vitro* by reducing cellular proliferation and promoting apoptosis[79]. In addition, a diet rich in fibre is associated with lower plasma levels of biomarkers of systemic inflammation such as TNF-α receptor-2 and IL-6,

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potentially affecting the carcinogenesis process[80]. Also, fibre itself may absorb carcinogens from food items that pass through the digestive tract[35], or reduce the risk of Barrett's oesophagus by decreasing the risk of hiatus hernia[81]. However, similar to carbohydrate intake, the possibility that a high-fibre 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 fibre and the risk of oesophageal adenocarcinoma. More studies are needed to evaluate the relationship between fibre intake and the risk of Barrett's oesophagus, and results from cohort studies will help shed light on the association with oesophageal 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-metabolising enzyme genotypes are associated with an increased risk of gastric cardia adenocarcinoma and oesophageal squamous cell carcinoma[84,85]. Also, folate deficiency has been hypothesised to increase the risk of cancer via mediation by p53 tumour suppressor gene[86], or by decreasing intracellular *S*-adenosylmethionine 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 B_6 on p53 mutations in oesophageal 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 oesophageal 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 oesophageal adenocarcinoma compared with 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 oesophagus, progression from Barrett's oesophagus into cancer, or the role of functional polymorphisms in genes encoding folate-metabolising enzymes on the risk of oesophageal adenocarcinoma or Barrett's oesophagus.

It is important to note that alcohol (a folate antagonist), smoking (which impairs folate status), and other methyl-related nutrients (for example, vitamin B_6, vitamin B_{12} and methionine) have an impact on 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 oesophageal adenocarcinoma. In summary, there is evidence that dietary folate may reduce the risk of oesophageal adenocarcinoma. Studies are needed to evaluate its effect on Barrett's oesophagus, progression from Barrett's oesophagus 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 oesophageal adenocarcinoma, and one has studied the association with Barrett's oesophagus. The results are mixed. In the EPIC prospective cohort study that involved a mean follow-up of 6·5 years and sixty-five newly diagnosed cases of oesophageal adenocarcinoma, a positive association was observed for processed meat (HR 3·54; 95 % CI 1·57, 7·99; T3 *v.* T1) while the result for total meat intake was not significant (HR 1·79; 95 % CI 0·86, 3·75; T3 *v.* T1)[91]. In a multicentre, population-based case–control study, total meat intake was associated with an increased risk of oesophageal adenocarcinoma (OR 1·43; 95 % CI 1·11, 1·83; per serving/d), with red meat most strongly related to disease risk (OR 2·49; 95 % CI 1·39, 4·46; per serving/d)[51]. In the same study population, animal protein intake was associated with an increased risk of oesophageal 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 oesophageal adenocarcinoma[35,36,54]. Also, a recent study of Barrett's oesophagus reported that total meat intake was inversely related to long-segment Barrett's oesophagus (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 oesophageal 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 (for example, fat, protein, Fe), nitrite/nitrate content, and/or meat preparation methods (for example, cooking or preserving methods). Meats cooked at high temperatures (i.e. frying and grilling) and for a long duration contain heterocyclic amines and polycyclic aromatic hydrocarbons, potent mutagens that have been shown to induce tumours in animal models[89]. Total heterocyclic amine intake was positively associated with the risk of upper aerodigestive tract cancers in a study conducted in Uruguay[92]. However, existing studies of oesophageal adenocarcinoma and Barrett's oesophagus 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 oesophageal cancers[95]. *N*-nitroso compounds are strong animal

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carcinogens and have been shown to cause cancers of the nasal cavity, oesophagus 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 oesophageal adenocarcinoma, the US multicentre 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 oesophageal 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 oesophageal adenocarcinoma compared with 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 oesophagus or progression. Since pesticides on fruits and vegetables are another major source of nitrate, the effects of nitrite/nitrate exposure on disease risk have significant public health implications and should be considered before encouraging high-risk individuals to indiscriminantly consume large amounts of fruits and vegetables.

In sum, evidence from cohort studies suggests an adverse association between meat intake and the risk of oesophageal adenocarcinoma, particularly for red meat and processed meat. Further research is needed to evaluate types of meat and the risk of Barrett's oesophagus, and the role of nitrite and nitrate, heterocyclic amines and polycyclic aromatic hydrocarbons in the aetiology of oesophageal adenocarcinoma and Barrett's oesophagus.

Fat

Given the established relationships between obesity and the risk of Barrett's oesophagus and oesophageal 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 oesophagus[100,101]. Among the seven case–control studies that evaluated the association between fat intake and the risk of oesophageal adenocarcinoma, four reported an increased risk among individuals with high total fat intake compared with 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 oesophagus 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 oesophagus as measured by DNA content flow cytometry[62].

The discrepancy in findings between studies may come from a 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 oesophagus into oesophageal adenocarcinoma[104].

On the other hand, PUFA and *n*-3 fatty acids, mainly found in plants and fish, may decrease the risk of oesophageal adenocarcinoma. *n*-3 Fatty acids have been found to reduce cyclo-oxygenase 2 (COX-2) protein concentrations in Barrett's tissues in a small randomised study[105]. Up-regulation of COX-2 has been shown to occur in both Barrett's oesophagus and oesophageal 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 oesophageal adenocarcinoma and Barrett's oesophagus 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 oesophageal adenocarcinoma[29], and a study of Barrett's oesophagus reported an adverse association with *trans*-fat and saturated fat intake when examined continuously (data not shown), while *n*-3 fatty acids were inversely related to the risk of Barrett's oesophagus[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 *n*-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 oesophageal adenocarcinoma and Barrett's oesophagus.

Carbonated soft drinks

Carbonated soft drinks have been suggested as a risk factor for oesophageal adenocarcinoma because they are acidic and may increase reflux by reducing oesophageal 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 oesophageal adenocarcinoma, two large case–control studies in Sweden and Australia have reported no relationship[111,112]. In contrast, a US multicentre study reported a strong inverse relationship between carbonated soft drink intake and oesophageal adenocarcinoma (OR 0·47; 95 % CI 0·29, 0·76)[113]. Therefore, the current data show no conclusive evidence that soft drink consumption increases the risk of oesophageal adenocarcinoma, and no studies have evaluated its relationship with Barrett's oesophagus or progression of Barrett's oesophagus into cancer.

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Iron

In animal models, Fe supplementation before reflux-induced oesophageal injury substantially increased the risk of oesophageal metaplasia and oesophageal adenocarcinoma, and the cells in these models demonstrated oxidative damage[26,114]. In addition, the effect of Fe on oesophageal adenocarcinoma aetiology has been hypothesised because males are at higher risk for oesophageal adenocarcinoma and Barrett's oesophagus, and they typically have higher Fe saturation levels compared with females[115–117].

However, the epidemiological evidence related to Fe and the risk of oesophageal adenocarcinoma or Barrett's oesophagus is not consistent with the hypothesis that Fe 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 oesophagus also reported that levels of dietary Fe and serum Fe stores (ferritin and transferrin saturation) were lower among cases[118]. In sum, there is currently no evidence that dietary Fe intake or Fe stores are adversely associated with the risk of oesophageal adenocarcinoma or Barrett's oesophagus. 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 fibre 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 epidemiological studies makes it difficult to pinpoint the dietary component most likely to influence disease aetiology. 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 oesophageal adenocarcinoma and one has reported on the association with Barrett's oesophagus. A Swedish study reported that a 'healthy' dietary pattern characterised by a high intake of vegetables, fruits, fish and poultry was associated with a lower risk of oesophageal adenocarcinoma, and that a Western-style diet rich in processed meat, red meat, sweets and fast foods was associated with an increased risk of oesophageal 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 oesophageal adenocarcinoma risk (OR 3·6; 95 % CI 0·96, 13·2)[54]. A case–control study of Barrett's oesophagus 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 characterised 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, fibre and Fe and the risk of oesophageal adenocarcinoma, and to a lesser degree, Barrett's oesophagus. There is limited evidence that folate is inversely related and red meat and processed meat are positively related to the risk of oesophageal adenocarcinoma. The current evidence does not support the hypothesis that carbonated beverages are associated with a higher risk of oesophageal adenocarcinoma, and the data are inconclusive about vitamin E, Se, vitamin supplement intake, various fatty acids, nitrite/nitrate and heterocyclic amines. The finding of diet–disease relationships for both Barrett's oesophagus and oesophageal adenocarcinoma suggests that these dietary factors may act early in the carcinogenic pathway, rather than by decreasing the likelihood of Barrett's oesophagus transforming into oesophageal adenocarcinoma. Diet could, for example, alter the risk of gastro-oesophageal reflux itself or, among individuals with reflux-induced damage, change their risk of developing Barrett's oesophagus. Patients at higher risk for Barrett's oesophagus and oesophageal 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 oesophagus to oesophageal adenocarcinoma, and on the influence of diet, particularly micronutrients, on the risk of Barrett's oesophagus. Further evidence from cohort studies will help determine whether randomised chemoprevention trials would be warranted.

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