Published in final edited form as:

Best Pract Res Clin Gastroenterol. 2015 February ; 29(1): 29–39. doi:10.1016/j.bpg.2014.11.008.

A review of the epidemiology of Barrett's oesophagus and oesophageal adenocarcinoma

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Abstract

While the incidence rates of many cancers have decreased in past decades, the incidence of oesophageal adenocarcinoma continues to increase. The only known precursor for oesophageal adenocarcinoma is Barrett's oesophagus. Studies conducted have identified white race, male sex, GORD, cigarette smoking, obesity, and the absence of *Helicobacter pylori* status as risk factors for oesophageal adenocarcinoma. Other potential associations include dietary factors and the absence of non-steroidal anti-inflammatory drug use. Many individual studies have been limited by sample size and several meta-analyses have pooled data from studies to address this limitation. In this review we present a synthesis of these studies and summarize current knowledge of risk factors for both oesophageal adenocarcinoma and Barrett's oesophagus.

Keywords

Barrett's oesophagus; Oesophageal adenocarcinoma; Epidemiology; Risk factors

Introduction

While incidence rates for most cancers have been decreasing in the US, the incidence of oesophageal adenocarcinoma has increased greater than six-fold over the last four decades [1]. Barrett's oesophagus, a metaplastic transformation from the normal squamous mucosa of the oesophagus to a columnar lining, is the only known precursor for oesophageal adenocarcinoma; its presence conveys a 30–40 fold increased risk of oesophageal adenocarcinoma [2–6]. In a meta-analysis of 29 studies of Barrett's oesophagus, the incidence rate of oesophageal adenocarcinoma among persons with Barrett's oesophagus was 5.3 per 1000 person years, when early incident cancers were excluded [7]. The true prevalence of Barrett's oesophagus is unknown, but it is estimated to affect 1.6 to 6.8 percent of people [8]. Given the magnitude of increase in risk for oesophageal adenocarcinoma among persons with Barrett's oesophagus, identifying, understanding and

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Conflict of interest

None.

intervening on potentially modifiable risk factors could have a major impact on the rate of oesophageal adenocarcinoma. Currently, only about 5% of patients diagnosed with oesophageal adenocarcinoma have a pre-cancer diagnosis of Barrett's oesophagus [9]. Thus, if risk factor modification in the general population decreased cancer risk by only 10%, it would be twice as effective as a perfect intervention that eliminated cancer risk among all persons with known Barrett's oesophagus. Alternatively, identifying risk factors could aid in the development of models to more efficiently screen patients for Barrett's oesophagus (if surveillance and post-diagnosis interventions are shown to be effective) [10,11].

Many studies of various size and design have been conducted in the past two decades to better understand the aetiology of and risk factors for oesophageal adenocarcinoma and Barrett's oesophagus. Generally agreed upon risk factors for oesophageal adenocarcinoma, based on the results of these studies, are white race, male sex, gastro-oesophageal reflux disease (GORD), cigarette smoking (and history of smoking), obesity, and *Helicobacter pylori* (*H. pylori*) status. Other potential risk factors that have been studied, with less consistent results, include alcohol, dietary factors, and use of non-steroidal anti-inflammatory drugs (NSAIDs). The most frequently described limitations of these studies are sample size (given the relative rarity of oesophageal adenocarcinoma) and identification of appropriate comparison groups, the former of which limits the power to study gender specific roles of potential risk factors. To address this limitation, several meta-analyses have pooled data from recent studies to study some of the possible risk factors at a more granular level. In particular, the Barrett's Oesophagus and Oesophageal Adenocarcinoma Consortium (BOACON), supported by the National Cancer Institute, has pooled data from 13 population-based case-control and two prospective cohort studies to assess risk factors for oesophageal adenocarcinoma and Barrett's oesophagus [12–26]. (Table 1) We herein describe studies of several risk factors and present data syntheses of, typically meta-analyses, provided by different investigators, including those from BOACON. Much information has been disseminated since a prior review was published on epidemiologic risk factors for Barrett's oesophagus and adenocarcinoma [27]. In this review we present results of studies of both Barrett's oesophagus and oesophageal adenocarcinoma; risk factors which are present for both Barrett's oesophagus and cancer may act early in the carcinogenic pathway whereas those that are present only for oesophageal adenocarcinoma may represent risk factors for the transition from Barrett's oesophagus to cancer. We include the gender-specific risk of Barrett's oesophagus and oesophageal adenocarcinoma for each factor studied whenever detailed data from multiple publications are available.

Risk factors

Demographics

The incidence of both Barrett's oesophagus and oesophageal adenocarcinoma increase with age, however as much Barrett's oesophagus is asymptomatic it is difficult to determine when Barrett's oesophagus first develops [28]. In a large population based cohort study of persons with Barrett's oesophagus, there was an increased risk of oesophageal adenocarcinoma for persons >50 years, but no trend for increasing magnitude of risk beyond age 50 [29]. Whites have twice the risk of oesophageal adenocarcinoma as Hispanics and a 3–4 fold increased

risk compared to blacks [30,31]. A prevalence study of Barrett's oesophagus conducted over one year in the US (by endoscopy) suggests that the prevalence among non-Hispanic whites is 6.1%, compared to 1.7% among Hispanics and 1.6% among blacks; thus, much of the differences in cancer risk by race/ethnicity may stem from differences in the risk of Barrett's oesophagus [32].

The male/female ratio of Barrett's oesophagus is approximately two to one [33]. In contrast, the incidence rate of oesophageal adenocarcinoma is three–eight times higher in males than in females, suggesting that men are not only more likely to get Barrett's oesophagus, but, once they have it, they may be more likely to then progress to cancer [33,34]. In a meta-analysis of studies of persons with Barrett's oesophagus the average pooled incidence of oesophageal adenocarcinoma for men (six studies) with Barrett's oesophagus was twice as high as for women (five studies) with Barrett's oesophagus (10.2/1000 person years vs. 4.5/1000 person years) [7]. That males are disproportionately affected by Barrett's oesophagus, in part explains why most individual studies conducted have not been sufficiently powered to address individual risk factors by gender, as small numbers of female cases are usually available for study.

While age, race, and sex are risk factors for both Barrett's oesophagus and oesophageal adenocarcinoma, demographic factors (particularly race and gender) appear to also increase the risk of progression from Barrett's oesophagus to oesophageal adenocarcinoma.

GORD

Gastro-oesophageal reflux disease is a known risk factor for both Barrett's oesophagus and oesophageal adenocarcinoma [35–37]. It has been estimated that approximately 10% of persons with GORD will develop Barrett's oesophagus [38]. GORD is also associated with oesophageal adenocarcinoma, persons with recurrent heartburn or regurgitation had approximately five times the risk of oesophageal adenocarcinoma as persons without symptoms in a recent meta-analysis [39]. The risk appears to increase with increasing duration and frequency of symptoms [37].

Helicobacter pylori

Evidence of prior infection with *H. pylori* has been inversely correlated with the risks of both Barrett's oesophagus and oesophageal adenocarcinoma. A pooled analysis of four fairly large studies of patients with Barrett's oesophagus with minimal selection and information biases (i.e. controls were derived from random samples of general adult populations or colonoscopy patients) suggested that the presence of *H. pylori* may decrease the risk of Barrett's oesophagus (OR: 0.46; 95% CI: 0.35–0.60); the mechanism may, in part, be from a reduced risk of GORD symptoms among persons with *H. pylori* [40,41]. Results were similar when analyses were confined to only studies in the United States ($n = 7$) in the meta-analysis (OR: 0.46; 95% CI: 0.40–0.53). The more virulent Cag A subtype of *H. pylori* also appeared to have an inverse association with Barrett's oesophagus (OR: 0.38; 95% CI: 0.19–0.78). Similar associations have been reported for *H. pylori* infection and oesophageal adenocarcinoma (OR: 0.57; 95% CI: 0.44–0.73) [42].

Alcohol

The general consumption of alcohol (any type) is not strongly correlated with an increased risk of either Barrett's oesophagus or oesophageal adenocarcinoma, at any level of alcohol intake. Even among persons consuming 7 drinks per day, no association was found (OR: 0.97; 95% CI: 0.68–1.36) with the risk of adenocarcinoma [43]. This is in contrast to oesophageal squamous cell carcinoma, where alcohol is a known strong risk factor for the development of disease. In contrast, a modest, inverse association with oesophageal adenocarcinoma has been observed with moderate intake (0.5–<1 drink/day), similar to what has been found in studies of alcohol consumption and risk of Barrett's oesophagus, in particular for wine consumption [44,45]. This finding could be due to chance or may be a marker for unmeasured or incomplete adjustment for habits of healthy living. Further exploration into types of alcohol and moderate intake is warranted.

Smoking

Smoking is associated with an increased risk of both Barrett's oesophagus and oesophageal adenocarcinoma. While individual studies of smoking and Barrett's oesophagus suggest that smoking is not a strong risk factor for Barrett's oesophagus [46,47], a meta-analysis of five studies found that ever smoking was a risk factor for Barrett's oesophagus, both when patients were compared to persons with GORD and to population controls; a trend of increasing risk with increased pack-years smoked was also observed.

Current smokers also have an increased risk of oesophageal adenocarcinoma, compared to non-smokers (OR: 1.96; 95% CI: 1.64–2.34) [48]. A dose-response relationship exists, as pack years smoked increases so does the risk of oesophageal adenocarcinoma ($p < 0.001$). The strength of the association appears to be modified by gender and duration of smoking cessation. Men that ever smoked had a slightly higher risk of oesophageal adenocarcinoma (OR: 2.10; 95% CI: 1.71–2.59) than women (OR: 1.74; 95% CI: 1.21–2.51). The magnitude of risk appears to go down after smoking cessation, however persons that quit smoking cigarettes 10 years prior still had a higher risk of oesophageal adenocarcinoma than never smokers (OR: 1.72; 95% CI: 1.38, 2.15). Ongoing smoking also increases the risk of Barrett's oesophagus progressing to cancer, creating a potentially modifiable risk factor for patients identified with Barrett's oesophagus [49]. Plausible biological mechanisms for the association between smoking and progression to cancer include genotoxicity of tobacco smoke, an increase in prevalence of GORD among smokers, and increasing amounts of nitrosamines in cigarettes. The decline in smoking in recent decades, while the incidence of oesophageal adenocarcinoma has still drastically increased, suggests that cigarette smoking alone, accounts for only a modest percentage of cases or provides a long latency of increased risk. The latter is possible if smoking primarily acts to increase the risk of Barrett's oesophagus, which then progresses to cancer only decades later.

Diet

Various dietary factors appear to be associated with both Barrett's oesophagus and oesophageal adenocarcinoma, based on results of several studies that have looked at specific dietary factors and patterns. Omega-3-fatty acids, polyunsaturated fat, total fibre, fibre from fruits and vegetables, dietary vitamin C and beta-carotene, and vitamin E appear to be

associated with a lower risk of Barrett's oesophagus [50,51]. An overall 'health-conscious' diet, described as a diet high in fruits, vegetables, and non-fried fish appears to be protective of Barrett's oesophagus (OR: 0.35; 95% CI: 0.20–0.64) compared to a 'Western' diet which is higher in fast foods and meat [52]. Conversely, persons with higher transfat intakes tend to have an increased risk of Barrett's oesophagus [50]. A meta-analysis of antioxidant intake and oesophageal adenocarcinoma found results consistent with studies of Barrett's oesophagus, where higher intakes of vitamin C, beta-carotene, vitamin A, and vitamin E were all associated with a lower risk of oesophageal adenocarcinoma [53]. A previously conducted review of the literature for dietary factors and risk of oesophageal adenocarcinoma thus suggested that patients at a higher risk for Barrett's oesophagus and oesophageal adenocarcinoma may benefit from a reduction in consumption of red meat and an increase in consumption of fruits and vegetables [54]. Fibre, known to have anti-carcinogenic effects, reduces the risk of oesophageal adenocarcinoma. Those with highest fibre intakes had a lower risk of oesophageal adenocarcinoma, compared to those with lowest levels of intake (OR: 0.66; 95% CI: 0.44–0.92) [55]. In this same study, there was a 60–66% reduction in risk of Barrett's oesophagus in the group with the highest levels of fibre intake. Proposed mechanisms for the effect of fibre on Barrett's oesophagus and oesophageal adenocarcinoma are via reduction of GORD and the presence of phytic acid in high fibre foods decreasing cellular proliferation and which promote apoptosis, and inhibits oesophageal adenocarcinoma cell growth.

Aspirin/NSAIDS

Aspirin and NSAID use are associated with an overall decreased risk of oesophageal adenocarcinoma; users of NSAIDs have a decreased risk of oesophageal adenocarcinoma (OR: 0.68; 95% CI: 0.56–0.83) compared to non-users [56]. There appears to be a decrease in risk with increasing frequency of use, but no trend in risk with increase duration of use. The ever-use of aspirin was associated with a 23% reduction in risk of oesophageal adenocarcinoma among current users, and non-aspirin NSAIDs had a similar, but somewhat lower reduction in oesophageal adenocarcinoma (OR: 0.81; 95% CI: 0.67–0.96). Findings from other pooled analyses are consistent [57,58].

The mechanism for a decrease in cancer risk may be through a decreased risk of Barrett's oesophagus, although there are relatively few studies of the associations between aspirin/NSAIDs and the risk of Barrett's oesophagus, and they have conflicting results. Some studies have found a decrease in the risk of Barrett's oesophagus among aspirin users [59,60]. In contrast, others have found no association between NSAID use and the presence of Barrett's oesophagus and suggested that the protective mechanism of NSAIDs on cancer may occur subsequent to the development of Barrett's oesophagus. One case-control study, found that Barrett's oesophagus cases were less likely to have used aspirin than controls (OR: 0.53; 95% CI: 0.31–0.90). The results of this study suggest that aspirin may work early in the disease pathway, as the association with oesophageal adenocarcinoma was similar to that with Barrett's oesophagus [61], although the potential for aspirin also decreasing the risk of progression of Barrett's was supported by a meta-analysis of studies that evaluated the risk of neoplastic progression. That study found a reduced risk of progression to high grade dysplasia or cancer among both aspirin users (RR: 0.63; 95% CI: 0.43–0.94) and non-

aspirin NSAID users (RR = 0.50; 95% CI: 0.32–0.78) [62]. A trial of aspirin for decreasing the risk of neoplastic progression is currently underway in the United Kingdom [63].

An inverse association between aspirin/NSAID use and Barrett's oesophagus is biologically plausible. Aspirin/NSAID use is associated with a reduction in the risk of other cancers and precancerous lesions, such as colon adenomas [64–67]; however, adenomas already represent a dysplastic condition and less is known about how aspirin/NSAIDs may modify the development of metaplasia, such as is found with Barrett's oesophagus. Potential mechanisms for modifying a metaplastic response to inflammation include the inhibition of prostaglandin production [68]. Supporting this hypothesis, animal models of reflux suggest that anti-inflammatory medications can both decrease the risk of oesophagitis resulting from reflux-induced damage and the risk of Barrett's-like changes [69,70].

Obesity and body composition

Obesity is one of the strongest risk factors for many cancers and while obesity is associated with oesophageal adenocarcinoma, BMI does not appear to be an independent risk factor for Barrett's oesophagus [23]. Among patients with GORD, there is no association between increasing BMI and progression to Barrett's oesophagus [71]. However, waist circumference (a marker of adiposity), is associated with Barrett's oesophagus in both men and women, even when adjusted for BMI [72].

Obesity is also associated with a higher risk of oesophageal adenocarcinoma; however, in contrast to Barrett's oesophagus, both BMI and increasing abdominal obesity are associated with cancer risk [73]. In a systematic review and meta-analyses, a BMI ≥ 25 was associated with an increased risk of oesophageal adenocarcinoma, in both males (OR: 2.2; 95% CI: 1.8–2.7) and females (OR: 1.9; 95% CI: 1.5–2.5) [74]. The risk was higher at higher BMIs, obese males and females had higher risk of oesophageal adenocarcinoma (OR: 2.4; 95% CI: 1.9–3.2 and OR: 1.9; 95% CI: 1.5–2.5, respectively) than did overweight males (OR: 1.8; 95% CI: 1.5–2.2) and females (OR: 1.5; 95% CI: 1.1–2.2). This study also found that the risk increased with increasing distance from the gastro-oesophageal junction (weaker associations were observed in cancers of the gastric cardia and gastro-oesophageal junction). Data syntheses also suggest a dose-response between risk of oesophageal adenocarcinoma and increasing BMI (p -trend <0.001) [75]. Those with a BMI ≥ 40 had almost five times the risk of oesophageal adenocarcinoma as persons of normal weight (OR: 4.76; 95% CI: 2.96–7.66). The results were similar when stratified by GORD and gender. They also found an interaction between BMI and GORD, persons with GORD and high BMI had the highest risk of oesophageal adenocarcinoma.

The proposed pathway by which BMI may increase the risk of oesophageal adenocarcinoma is not known; potential explanations include a mechanical increase in intra-abdominal pressure or alterations obesity-associated peptides (e.g. leptin, ghrelin, adiponectin and insulin-like growth factors) may also modify cell repair after injury, cell growth and gastric emptying [76,77]. A mechanical increase in GORD is not likely the sole mechanism based on available data from a meta-analysis, where the strength of the relationship between BMI and risk oesophageal adenocarcinoma were not altered when adjusted for presence of GORD symptoms [75]. The absence of mediation by GORD may suggest an indirect pro-

inflammatory route of association between BMI/abdominal obesity and oesophageal adenocarcinoma. Abdominal obesity is also an independent risk factor for progression from Barrett's oesophagus to cancer [49].

Hormonal status

The existing literature does not include data on the association of endogenous hormones and Barrett's oesophagus, but does suggest that breastfeeding may be associated with a decreased risk of oesophageal adenocarcinoma. A pooled analysis of women studied the potential effect of endogenous reproductive factors and exogenous hormones and their associations with the risk of oesophageal adenocarcinoma. They found a reduced risk of oesophageal adenocarcinoma among parous women after breastfeeding (OR: 0.42; 95% CI: 0.24–0.75) [78]. The risk appeared to decrease with an increased duration (>12 months) of breastfeeding (OR: 0.22; 95% CI: 0.10–0.52). However, no other factor studied was significantly associated with oesophageal adenocarcinoma (parity, menstruation, history of pregnancy, oral contraception use, and hormone replacement therapy). Lactation has been suggested as protective of other cancers in the past (stomach, pancreas, and gallbladder) [79–81]. A potential biological mechanism by which breastfeeding may be protective is via modification of endogenous hormones or their receptors. Oxytocin levels are higher when breastfeeding and can regulate tumour growth by activating oxytocin receptors [82].

Summary

There is an ever-growing literature describing risk factors for Barrett's oesophagus and oesophageal adenocarcinoma. Many risk factors are now known for Barrett's oesophagus and oesophageal adenocarcinoma (Table 2). Specifically, male sex, increasing age, white race, GORD symptoms, the absence of *H. pylori*, smoking, increasing abdominal obesity/BMI, and certain dietary factors have been shown to have positive associations with the development of Barrett's oesophagus or oesophageal adenocarcinoma in both individual case-control studies and meta-analyses. A few limitations still exist, namely most studies are largely restricted to non-Hispanic whites and results therefore are limited in their generalizability; however, the risk of these disorders is highest in white males. These data have informed the recent development of new models for identifying who is most likely to have Barrett's oesophagus and offer the potential for developing more precise risk prediction tools for who among that group is most likely to progress to oesophageal adenocarcinoma [10,11]. One of these tools, for example, using a score of demographics, traditional exposure risk factors and biomarkers (e.g. leptin and interleukins), found that, compared with persons with a score of 0, those with scores of at least three had over a 10-fold increased risk for Barrett's oesophagus (OR: 11.9; 95% CI: 4.06–34.9) [11]. Another model, using only the risk factors of GORD symptoms, abdominal obesity, tobacco use and age found a significant improvement in the ability to identify persons likely to have Barrett's oesophagus compared with a model based on GORD alone [10].

Future studies could expand on the knowledge obtained in individual case-control and GWAS studies which suggested obesity-associated peptides, height, and genetic susceptibility loci as risk factors [77,83–85]. Additional research into the role of moderate

alcohol intake on the risk of Barrett's oesophagus and oesophageal adenocarcinoma and the role of endogenous hormones and NSAIDs on Barrett's oesophagus may elicit modifiable risk factors or lifestyle factors. Finally, further research should explore why only certain persons with Barrett's oesophagus develop oesophageal adenocarcinoma, while the vast majority of persons with Barrett's oesophagus do not progress to oesophageal adenocarcinoma. Such research may offer the potential for developing interventions for patients with Barrett's oesophagus.

Acknowledgments

Role of funding source

This work was supported by the National Institutes of Health RO1 DK63616 (AK and DAC); 1R21DK077742.

References

1. Simard EP, Ward EM, Siegel R, Jemal A. Cancers with increasing incidence trends in the United States: 1999 through 2008. *CA Cancer J Clin*. 2012 Jan 4.62:118–28. Epub 2012/01/28. Eng. [PubMed: 22281605]
2. Sharma P, McQuaid K, Dent J, Fennerty MB, Sampliner R, Spechler S, et al. A critical review of the diagnosis and management of Barrett's esophagus: the AGA Chicago Workshop. *Gastroenterology*. 2004 Jul; 127(1):310–30. Epub 2004/07/06. eng. [PubMed: 15236196]
3. Shaheen NJ, Crosby MA, Bozymski EM, Sandler RS. Is there publication bias in the reporting of cancer risk in Barrett's esophagus? *Gastroenterology*. 2000 Aug; 119(2):333–8. Epub 2000/08/10. eng. [PubMed: 10930368]
4. Spechler SJ, Jain SK, Tendler DA, Parker RA. Racial differences in the frequency of symptoms and complications of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther*. 2002 Oct; 16(10): 1795–800. Epub 2002/09/25. eng. [PubMed: 12269973]
5. Reid BJ, Barrett MT, Galipeau PC, Sanchez CA, Neshat K, Cowan DS, et al. Barrett's esophagus: ordering the events that lead to cancer. *Eur J Cancer Prev*. 1996 Dec; 5(Suppl 2):57–65. Epub 1996/12/01. eng.
6. Jankowski JA, Provenzale D, Moayyedi P. Esophageal adenocarcinoma arising from Barrett's metaplasia has regional variations in the west. *Gastroenterology*. 2002 Feb; 122(2):588–90. Epub 2002/02/16. eng.
7. Yousef F, Cardwell C, Cantwell MM, Galway K, Johnston BT, Murray L. The incidence of esophageal cancer and high-grade dysplasia in Barrett's esophagus: a systematic review and meta-analysis. *Am J Epidemiol*. 2008 Aug 1; 168(3):237–49. Epub 2008/06/14. eng. [PubMed: 18550563]
8. Gilbert EW, Luna RA, Harrison VL, Hunter JG. Barrett's esophagus: a review of the literature. *J Gastrointest Surg*. 2011 May; 15(5):708–18. Epub 2011/04/05. eng. [PubMed: 21461873]
9. Corley DA, Levin TR, Habel LA, Weiss NS, Buffler PA. Surveillance and survival in Barrett's adenocarcinomas: a population-based study. *Gastroenterology*. 2002 Mar; 122(3):633–40. Epub 2002/03/05. eng. [PubMed: 11874995]
10. Rubenstein JH, Morgenstern H, Appelman H, Scheiman J, Schoenfeld P, McMahon LF Jr, et al. Prediction of Barrett's esophagus among men. *Am J Gastroenterol*. 2013 Mar; 108(3):353–62. Epub 2013/01/16. eng. [PubMed: 23318485]
11. Thrift AP, Garcia JM, El-Serag HB. A multibiomarker risk score helps predict risk for Barrett's esophagus. *Clin Gastroenterol Hepatol*. 2014 Aug; 12(8):1267–71. Epub 2013/12/24. eng. [PubMed: 24362047]
12. Brown LM, Silverman DT, Pottern LM, Schoenberg JB, Greenberg RS, Swanson GM, et al. Adenocarcinoma of the esophagus and esophagogastric junction in white men in the United States: alcohol, tobacco, and socioeconomic factors. *Cancer Causes Control CCC*. 1994 Jul; 5(4):333–40. Epub 1994/07/01. eng. [PubMed: 8080945]

13. Vaughan TL, Davis S, Kristal A, Thomas DB. Obesity, alcohol, and tobacco as risk factors for cancers of the esophagus and gastric cardia: adenocarcinoma versus squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev*. 1995 Mar; 4(2):85–92. Epub 1995/03/01. eng. [PubMed: 7742727]
14. Gammon MD, Schoenberg JB, Ahsan H, Risch HA, Vaughan TL, Chow WH, et al. Tobacco, alcohol, and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia. *J Natl Cancer Inst*. 1997 Sep 3; 89(17):1277–84. Epub 1997/09/18. eng. [PubMed: 9293918]
15. Lagergren J, Bergstrom R, Lindgren A, Nyren O. The role of tobacco, snuff and alcohol use in the aetiology of cancer of the oesophagus and gastric cardia. *Int J Cancer*. 2000 Feb 1; 85(3):340–6. Epub 2000/02/01. eng. [PubMed: 10652424]
16. Cheng KK, Sharp L, McKinney PA, Logan RF, Chilvers CE, Cook-Mozaffari P, et al. A case-control study of oesophageal adenocarcinoma in women: a preventable disease. *Br J Cancer*. 2000 Jul; 83(1):127–32. Epub 2000/07/07. eng. [PubMed: 10883680]
17. Wu AH, Wan P, Bernstein L. A multiethnic population-based study of smoking, alcohol and body size and risk of adenocarcinomas of the stomach and esophagus (United States). *Cancer Causes control CCC*. 2001 Oct; 12(8):721–32. Epub 2001/09/20. eng. [PubMed: 11562112]
18. Chen H, Ward MH, Graubard BI, Heineman EF, Markin RM, Potischman NA, et al. Dietary patterns and adenocarcinoma of the esophagus and distal stomach. *Am J Clin Nutr*. 2002 Jan; 75(1):137–44. Epub 2002/01/05. eng. [PubMed: 11756071]
19. Veugelaers PJ, Porter GA, Guernsey DL, Casson AG. Obesity and lifestyle risk factors for gastroesophageal reflux disease, Barrett esophagus and esophageal adenocarcinoma. *Dis Esophagus*. 2006; 19(5):321–8. Epub 2006/09/21. eng. [PubMed: 16984526]
20. Anderson LA, Watson RG, Murphy SJ, Johnston BT, Comber H, Mc Guigan J, et al. Risk factors for Barrett's oesophagus and oesophageal adenocarcinoma: results from the FINBAR study. *World J Gastroenterol WJG*. 2007 Mar 14; 13(10):1585–94. Epub 2007/04/28. eng. [PubMed: 17461453]
21. Whiteman DC, Sadeghi S, Pandeya N, Smithers BM, Gotley DC, Bain CJ, et al. Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus. *Gut*. 2008 Feb; 57(2):173–80. Epub 2007/10/13. eng. [PubMed: 17932103]
22. Freedman ND, Abnet CC, Leitzmann MF, Mouw T, Subar AF, Hollenbeck AR, et al. A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. *Am J Epidemiol*. 2007 Jun 15; 165(12):1424–33. Epub 2007/04/11. eng. [PubMed: 17420181]
23. Corley DA, Kubo A, Levin TR, Block G, Habel L, Zhao W, et al. Abdominal obesity and body mass index as risk factors for Barrett's esophagus. *Gastroenterology*. 2007 Jul; 133(1):34–41. quiz 311. Epub 2007/07/17. eng. [PubMed: 17631128]
24. Smith KJ, O'Brien SM, Green AC, Webb PM, Whiteman DC. Current and past smoking significantly increase risk for Barrett's esophagus. *Clin Gastroenterol Hepatol*. 2009; 7(8):840–8. [PubMed: 19410015]
25. Edelstein ZR, Farrow DC, Bronner MP, Rosen SN, Vaughan TL.
26. Corley DA, Kubo A, Zhao W. Abdominal obesity, ethnicity and gastro-oesophageal reflux symptoms. *Gut*. 2007 Jun; 56(6):756–62. Epub 2006/10/19. eng. [PubMed: 17047097]
27. Wong A, Fitzgerald RC. Epidemiologic risk factors for Barrett's esophagus and associated adenocarcinoma. *Clin Gastro-enterol Hepatol*. 2005 Jan; 3(1):1–10. Epub 2005/01/13. eng.
28. Corley DA, Kubo A, Levin TR, Block G, Habel L, Rumore G, et al. Race, ethnicity, sex and temporal differences in Barrett's oesophagus diagnosis: a large community-based study, 1994–2006. *Gut*. 2009 Feb; 58(2):182–8. Epub 2008/11/04. eng. [PubMed: 18978173]
29. Bhat S, Coleman HG, Yousef F, Johnston BT, McManus DT, Gavin AT, et al. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. *J Natl Cancer Inst*. 2011 Jul 6; 103(13):1049–57. Epub 2011/06/18. eng. [PubMed: 21680910]
30. Kubo A, Corley DA. Marked multi-ethnic variation of esophageal and gastric cardia carcinomas within the United States. *Am J Gastroenterol*. 2004 Apr; 99(4):582–8. Epub 2004/04/20. eng. [PubMed: 15089886]
31. El-Serag HB, Mason AC, Petersen N, Key CR. Epidemiological differences between adenocarcinoma of the oesophagus and adenocarcinoma of the gastric cardia in the USA. *Gut*. 2002 Mar; 50(3):368–72. Epub 2002/02/13. eng. [PubMed: 11839716]

32. Abrams JA, Fields S, Lightdale CJ, Neugut AI. Racial and ethnic disparities in the prevalence of Barrett's esophagus among patients who undergo upper endoscopy. *Clin Gastroenterol Hepatol*. 2008 Jan; 6(1):30–4. Epub 2007/12/08. eng. [PubMed: 18063419]
33. Cook MB, Wild CP, Forman D. A systematic review and meta-analysis of the sex ratio for Barrett's esophagus, erosive reflux disease, and nonerosive reflux disease. *Am J Epidemiol*. 2005 Dec 1; 162(11):1050–61. Epub 2005/10/14. eng. [PubMed: 16221805]
34. Kubo A, Corley DA. Marked regional variation in adenocarcinomas of the esophagus and the gastric cardia in the United States. *Cancer*. 2002 Nov 15; 95(10):2096–102. Epub 2002/11/02. eng. [PubMed: 12412162]
35. Spechler SJ, Goyal RK. The columnar-lined esophagus, intestinal metaplasia, and Norman Barrett. *Gastroenterology*. 1996 Feb; 110(2):614–21. Epub 1996/02/01. eng. [PubMed: 8566611]
36. McDougall NI, Johnston BT, Collins JS, McFarland RJ, Love AH. Three- to 4.5-year prospective study of prognostic indicators in gastro-oesophageal reflux disease. *Scand J Gastroenterol*. 1998 Oct; 33(10):1016–22. Epub 1998/11/26. eng. [PubMed: 9829353]
37. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med*. 1999 Mar 18; 340(11):825–31. Epub 1999/03/18. eng. [PubMed: 10080844]
38. Fennerty MB. Barrett's-related esophageal cancer: has the final hurdle been cleared, now paving the way for human chemoprevention trials? *Gastroenterology*. 2002 Apr; 122(4):1172–5. Epub 2002/03/23. eng. [PubMed: 11910370]
39. Cook MB, Corley DA, Murray LJ, Liao LM, Kamangar F, Ye W, et al. Gastroesophageal reflux in relation to adenocarcinomas of the esophagus: a pooled analysis from the Barrett's and esophageal adenocarcinoma consortium (BEACON). *PLoS One*. 2014; 9(7):e103508. Epub 2014/07/31. eng. [PubMed: 25075959]
40. Fischbach LA, Nordenstedt H, Kramer JR, Gandhi S, Dick-Onuoha S, Lewis A, et al. The association between Barrett's esophagus and *Helicobacter pylori* infection: a meta-analysis. *Helicobacter*. 2012 Jun; 17(3):163–75. Epub 2012/04/21. eng. [PubMed: 22515353]
41. Corley DA, Kubo A, Levin TR, Block G, Habel L, Rumore G, et al. *Helicobacter pylori* and gastroesophageal reflux disease: a case-control study. *Helicobacter*. 2008 Oct; 13(5):352–60. Epub 2009/03/03. eng. [PubMed: 19250510]
42. Nie S, Chen T, Yang X, Huai P, Lu M. Association of *Helicobacter pylori* infection with esophageal adenocarcinoma and squamous cell carcinoma: a meta-analysis. *Dis Esophagus*. 2014 Mar 17; 27:645–53. Epub 2014/03/19. Eng. [PubMed: 24635571]
43. Freedman ND, Murray LJ, Kamangar F, Abnet CC, Cook MB, Nyren O, et al. Alcohol intake and risk of oesophageal adenocarcinoma: a pooled analysis from the BEACON Consortium. *Gut*. 2011 Mar 14; 60(8):1029–37. Epub 2011/03/17. Eng. [PubMed: 21406386]
44. Kubo A, Levin TR, Block G, Rumore GJ, Quesenberry CP Jr, Buffler P, et al. Alcohol types and sociodemographic characteristics as risk factors for Barrett's esophagus. *Gastroenterology*. 2009 Mar; 136(3):806–15. Epub 2008/12/30. eng. [PubMed: 19111726]
45. Anderson LA, Cantwell MM, Watson RG, Johnston BT, Murphy SJ, Ferguson HR, et al. The association between alcohol and reflux esophagitis, Barrett's esophagus, and esophageal adenocarcinoma. *Gastroenterology*. 2009 Mar; 136(3):799–805. Epub 2009/01/24. eng. [PubMed: 19162028]
46. Kubo A, Levin TR, Block G, Rumore G, Quesenberry CP Jr, Buffler P, et al. Cigarette smoking and the risk of Barrett's esophagus. *Cancer Causes Control*. 2009 Apr; 20(3):303–11. Epub 2008/10/15. eng. [PubMed: 18853262]
47. Thrift AP, Kramer JR, Richardson PA, El-Serag HB. No significant effects of smoking or alcohol consumption on risk of Barrett's esophagus. *Dig Dis Sci*. 2014 Jan; 59(1):108–16. Epub 2013/10/12. eng. [PubMed: 24114046]
48. Cook MB, Kamangar F, Whiteman DC, Freedman ND, Gammon MD, Bernstein L, et al. Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: a pooled analysis from the international BEACON consortium. *J Natl Cancer Inst*. 2010 Sep 8; 102(17):1344–53. Epub 2010/08/19. eng. [PubMed: 20716718]

49. Hardikar S, Onstad L, Blount PL, Odze RD, Reid BJ, Vaughan TL. The role of tobacco, alcohol, and obesity in neoplastic progression to esophageal adenocarcinoma: a prospective study of Barrett's esophagus. *PLoS One*. 2013; 8(1):e52192. Epub 2013/01/10. eng. [PubMed: 23300966]
50. Kubo A, Block G, Quesenberry CP Jr, Buffler P, Corley DA. Effects of dietary fiber, fats, and meat intakes on the risk of Barrett's esophagus. *Nutr Cancer*. 2009; 61(5):607–16. Epub 2009/10/20. eng. [PubMed: 19838934]
51. Kubo A, Levin TR, Block G, Rumore GJ, Quesenberry CP Jr, Buffler P, et al. Dietary antioxidants, fruits, and vegetables and the risk of Barrett's esophagus. *Am J Gastroenterol*. 2008 Jul; 103(7): 1614–23. quiz 24. Epub 2008/05/23. eng. [PubMed: 18494834]
52. Kubo A, Levin TR, Block G, Rumore GJ, Quesenberry CP Jr, Buffler P, et al. Dietary patterns and the risk of Barrett's esophagus. *Am J Epidemiol*. 2008 Apr 1; 167(7):839–46. Epub 2008/01/26. eng. [PubMed: 18218607]
53. Kubo A, Corley DA. Meta-analysis of antioxidant intake and the risk of esophageal and gastric cardia adenocarcinoma. *Am J Gastroenterol*. 2007 Oct; 102(10):2323–30. quiz 31. Epub 2007/06/22. eng. [PubMed: 17581269]
54. Kubo A, Corley DA, Jensen CD, Kaur R. Dietary factors and the risks of oesophageal adenocarcinoma and Barrett's oesophagus. *Nutr Res Rev*. 2010 Dec; 23(2):230–46. Epub 2010/07/14. eng. [PubMed: 20624335]
55. Coleman HG, Murray LJ, Hicks B, Bhat SK, Kubo A, Corley DA, et al. Dietary fiber and the risk of precancerous lesions and cancer of the esophagus: a systematic review and meta-analysis. *Nutr Rev*. 2013 Jul; 71(7):474–82. Epub 2013/07/03. eng. [PubMed: 23815145]
56. Liao LM, Vaughan TL, Corley DA, Cook MB, Casson AG, Kamangar F, et al. Nonsteroidal anti-inflammatory drug use reduces risk of adenocarcinomas of the esophagus and esophagogastric junction in a pooled analysis. *Gastroenterology*. 2012 Mar; 142(3):442–52. e5. quiz e22–3. Epub 2011/11/24. eng. [PubMed: 22108196]
57. Abnet CC, Freedman ND, Kamangar F, Leitzmann MF, Hollenbeck AR, Schatzkin A. Non-steroidal anti-inflammatory drugs and risk of gastric and oesophageal adenocarcinomas: results from a cohort study and a meta-analysis. *Br J Cancer*. 2009 Feb 10; 100(3):551–7. Epub 2009/01/22. eng. [PubMed: 19156150]
58. Corley DA, Kerlikowske K, Verma R, Buffler P. Protective association of aspirin/NSAIDs and esophageal cancer: a systematic review and meta-analysis. *Gastroenterology*. 2003 Jan; 124(1):47–56. Epub 2003/01/04. eng. [PubMed: 12512029]
59. Omer ZB, Ananthakrishnan AN, Nattinger KJ, Cole EB, Lin JJ, Kong CY, et al. Aspirin protects against Barrett's esophagus in a multivariate logistic regression analysis. *Clin Gastroenterol Hepatol*. 2012 Jul; 10(7):722–7. Epub 2012/03/20. eng. [PubMed: 22426086]
60. Khalaf N, Nguyen T, Ramsey D, El-Serag HB. Nonsteroidal anti-inflammatory drugs and the risk of Barrett's esophagus. *Clin Gastroenterol Hepatol*. 2014 Apr 30; 12:1832–1839. e6. Epub 2014/05/06. Eng. [PubMed: 24793026]
61. Anderson LA, Johnston BT, Watson RG, Murphy SJ, Ferguson HR, Comber H, et al. Nonsteroidal anti-inflammatory drugs and the esophageal inflammation-metaplasia-adenocarcinoma sequence. *Cancer Res*. 2006 May 1; 66(9):4975–82. Epub 2006/05/03. eng. [PubMed: 16651456]
62. Zhang S, Zhang XQ, Ding XW, Yang RK, Huang SL, Kastelein F, et al. Cyclooxygenase inhibitors use is associated with reduced risk of esophageal adenocarcinoma in patients with Barrett's esophagus: a meta-analysis. *Br J Cancer*. 2014 Apr 29; 110(9):2378–88. Epub 2014/03/22. eng. [PubMed: 24651385]
63. Das D, Chilton AP, Jankowski JA. Chemoprevention of oesophageal cancer and the AspECT trial. *Recent Results Cancer Res*. 2009; 181:161–9. Epub 2009/02/14. eng. [PubMed: 19213566]
64. Ruder EH, Laiyemo AO, Graubard BI, Hollenbeck AR, Schatzkin A, Cross AJ. Non-steroidal anti-inflammatory drugs and colorectal cancer risk in a large, prospective cohort. *Am J Gastroenterol*. 2011 Jul; 106(7):1340–50. Epub 2011/03/17. eng. [PubMed: 21407185]
65. Pasricha PJ, Bedi A, O'Connor K, Rashid A, Akhtar AJ, Zahurak ML, et al. The effects of sulindac on colorectal proliferation and apoptosis in familial adenomatous polyposis. *Gastroenterology*. 1995 Sep; 109(3):994–8. Epub 1995/09/01. eng. [PubMed: 7657130]

66. Nugent KP, Farmer KC, Spigelman AD, Williams CB, Phillips RK. Randomized controlled trial of the effect of sulindac on duodenal and rectal polyposis and cell proliferation in patients with familial adenomatous polyposis. *Br J Surg*. 1993 Dec; 80(12):1618–9. Epub 1993/12/01. eng. [PubMed: 8298943]
67. Labayle D, Fischer D, Vielh P, Drouhin F, Pariente A, Bories C, et al. Sulindac causes regression of rectal polyps in familial adenomatous polyposis. *Gastroenterology*. 1991 Sep; 101(3):635–9. Epub 1991/09/01. eng. [PubMed: 1650315]
68. Thun MJ, Henley SJ, Patrono C. Nonsteroidal anti-inflammatory drugs as anticancer agents: mechanistic, pharmacologic, and clinical issues. *J Natl Cancer Inst*. 2002 Feb 20; 94(4):252–66. Epub 2002/02/21. eng. [PubMed: 11854387]
69. Buttar NS, Wang KK, Leontovich O, Westcott JY, Pacifico RJ, Anderson MA, et al. Chemoprevention of esophageal adenocarcinoma by COX-2 inhibitors in an animal model of Barrett's esophagus. *Gastroenterology*. 2002 Apr; 122(4):1101–12. Epub 2002/03/23. eng. [PubMed: 11910360]
70. Esquivias P, Morandeira A, Escartin A, Cebrian C, Santander S, Esteva F, et al. Indomethacin but not a selective cyclooxygenase-2 inhibitor inhibits esophageal adenocarcinogenesis in rats. *World J Gastroenterol*. 2012 Sep 21; 18(35):4866–74. Epub 2012/09/25. eng. [PubMed: 23002358]
71. Cook MB, Greenwood DC, Hardie LJ, Wild CP, Forman D. A systematic review and meta-analysis of the risk of increasing adiposity on Barrett's esophagus. *Am J Gastroenterol*. 2008 Feb; 103(2): 292–300. Epub 2007/11/08. eng. [PubMed: 17986313]
72. Kubo A, Cook MB, Shaheen NJ, Vaughan TL, Whiteman DC, Murray L, et al. Sex-specific associations between body mass index, waist circumference and the risk of Barrett's esophagus: a pooled analysis from the international BEACON consortium. *Gut*. 2013 Jan 26; 62:1684–91. Epub 2013/01/29. Eng. [PubMed: 23355549]
73. Corley DA, Kubo A, Zhao W. Abdominal obesity and the risk of esophageal and gastric cardia carcinomas. *Cancer Epidemiol Biomarkers Prev*. 2008 Feb; 17(2):352–8. Epub 2008/02/13. eng. [PubMed: 18268119]
74. Kubo A, Corley DA. Body mass index and adenocarcinomas of the esophagus or gastric cardia: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2006 May; 15(5):872–8. Epub 2006/05/17. eng. [PubMed: 16702363]
75. Hoyo C, Cook MB, Kamangar F, Freedman ND, Whiteman DC, Bernstein L, et al. Body mass index in relation to oesophageal and oesophagogastric junction adenocarcinomas: a pooled analysis from the International BEACON Consortium. *Int J Epidemiol*. 2012 Dec; 41(6):1706–18. Epub 2012/11/14. eng. [PubMed: 23148106]
76. Duggan C, Onstad L, Hardikar S, Blount PL, Reid BJ, Vaughan TL. Association between markers of obesity and progression from Barrett's esophagus to esophageal adenocarcinoma. *Clin Gastroenterol Hepatol*. 2013 Aug; 11(8):934–43. Epub 2013/03/08. eng. [PubMed: 23466711]
77. de Martel C, Haggerty TD, Corley DA, Vogelman JH, Orentreich N, Parsonnet J. Serum ghrelin levels and risk of subsequent adenocarcinoma of the esophagus. *Am J Gastroenterol*. 2007 Jun; 102(6):1166–72. Epub 2007/03/24. eng. [PubMed: 17378911]
78. Cronin-Fenton DP, Murray LJ, Whiteman DC, Cardwell C, Webb PM, Jordan SJ, et al. Reproductive and sex hormonal factors and oesophageal and gastric junction adenocarcinoma: a pooled analysis. *Eur J Cancer*. 2010 Jul; 46(11):2067–76. Epub 2010/05/12. eng. [PubMed: 20456945]
79. Heuch I, Jacobsen BK, Albrektsen G, Kvale G. Reproductive factors and pancreatic cancer risk: a Norwegian cohort study. *Br J Cancer*. 2008 Jan 15; 98(1):189–93. Epub 2007/11/15. eng. [PubMed: 18000501]
80. Heuch I, Kvale G. Does breastfeeding affect the risk of gastric cancer? *Int J Cancer J Int du cancer*. 2003 Oct 10; 106(6):982–3. Epub 2003/08/15. eng.
81. Inoue M, Ito LS, Tajima K, Yamamura Y, Kodera Y, Takezaki T, et al. Height, weight, menstrual and reproductive factors and risk of gastric cancer among Japanese postmenopausal women: analysis by subsite and histologic subtype. *Int J cancer J Int du cancer*. 2002 Feb 20; 97(6):833–8. Epub 2002/02/22. eng.

82. Heinig MJ, Dewey KG. Health effects of breast feeding for mothers: a critical review. *Nutr Res Rev.* 1997 Jan; 10(1):35–56. Epub 1997/01/01. eng. [PubMed: 19094257]
83. Thrift AP, Risch HA, Onstad L, Shaheen NJ, Casson AG, Bernstein L, et al. Risk of esophageal adenocarcinoma decreases with height, based on consortium analysis and Confirmed by Mendelian Randomization. *Clin Gastroenterol Hepatol.* 2014 Feb 12;12:1667–1675. e1. Epub 2014/02/18. Eng. [PubMed: 24530603]
84. Corley DA, Kubo A, Levin TR, Habel L, Zhao W, Leighton P, et al. Iron intake and body iron stores as risk factors for Barrett's esophagus: a community-based study. *Am J Gastroenterol.* 2008 Dec; 103(12):2997–3004. Epub 2008/10/16. eng. [PubMed: 18853987]
85. Levine DM, Ek WE, Zhang R, Liu X, Onstad L, Sather C, et al. A genome-wide association study identifies new susceptibility loci for esophageal adenocarcinoma and Barrett's esophagus. *Nat Genet.* 2013 Dec; 45(12):1487–93. Epub 2013/10/15. eng. [PubMed: 24121790]

Practice points

- Gastro-oesophageal reflux disease, older age, male sex, non-Hispanic whites, increasing abdominal girth, the absence of prior infection with *Helicobacter pylori* are some of the strongest predictors of Barrett's oesophagus and/or oesophageal adenocarcinoma
- Risk prediction tools using risk factors can help identify who is more likely to have Barrett's oesophagus

Research agenda

- Modifiable risk factors that merit particular attention for trials of reducing risk of Barrett's progressing to cancer include aspirin/NSAIDs, acid reduction, smoking cessation, weight reduction and dietary alterations
- Evaluating current population-wide interventions on smoking cessation, weight reduction and dietary alterations may indicate whether these efforts modify the risk of Barrett's oesophagus and cancer over long periods and in developing countries

Table 1

Studies included in BOACON.

Study	Design	Country	Outcome (s) studied	Recruitment period
Population Health Study	Case-control	US	Cancer	1986–1989
Larynx, Oesophagus, and Oral Cavity Study	Case-control	US	Cancer	1983–1990
United States Multi-Center Study	Case-control	US	Cancer	1993–1995
Swedish Oesophageal Cancer Study	Case-control	Sweden	Cancer	1995–1997
United Kingdom Study of Oesophageal Adenocarcinoma in Women	Case-control	UK	Cancer	1993–1996
Los Angeles County Multi-ethnic Case-Control Study	Case-control	US	Cancer	1992–1997
Nebraska Health Study II	Case-control	US	Cancer	1988–1993
Nova Scotia Barrett Oesophagus Study	Case-control	Canada	Cancer	2001–2003
Australian Cancer Study	Case-control	Australia	Cancer	2001–2005
NIH-AARP Diet and Health Study	Cohort	US	Cancer	1995–1996
Kaiser Permanente Multiphasic Health Checkup Study	Cohort	US	Cancer	1964–1973
Factors Influencing the Barrett's Adenocarcinoma Relationship Study	Case-control	Ireland	Cancer/Barrett's Oesophagus	2002–2004
Epidemiology and Incidence of Barrett's Oesophagus	Case-control	US	Barrett's Oesophagus	2002–2005
Study of Reflux Disease	Case-control	US	Barrett's Oesophagus	1997–2000
Epidemiology Case-Control Study of Barrett's Oesophagus	Case-control	US	Barrett's Oesophagus	2002–2007
Study of Digestive Health	Case-control	Australia	Barrett's Oesophagus	2003–2006

Table 2

Summary of factors studied and their association with Barrett's oesophagus and oesophageal adenocarcinoma.

Risk factor	Barrett's Oesophagus	Oesophageal adenocarcinoma
	Direction of association	
Age	+	+
Sex	+ (Male)	+ (Male)
Race	+ (White)	+ (White)
GORD	+	+
<i>H. pylori</i>	–	–
Smoking	+	+
Total alcohol intake	None	None
BMI	None	+
Waist circumference	+	+
Dietary factors		
Dietary fibre, vitamin C, diets high in fruits/vegetables/fish	–	–
Beta-carotene, vitamin A	?	–
Omega-3-fatty acids, polyunsaturated fat, vitamin E,	–	?
High trans fats/red meat	+	+
NSAIDS	?	–
Hormonal status	?	–