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BARRETT'S OESOPHAGUS: EPIDEMIOLOGY, CANCER RISK AND IMPLICATIONS FOR MANAGEMENT

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Abstract

Although endoscopic surveillance of patients with Barrett's oesophagus has been widely implemented, its effectiveness is debatable. The recently reported low annual oesophageal adenocarcinoma risk in population studies, the failure to identify most Barrett's patients at risk of disease progression, the poor adherence to surveillance and biopsy protocols, and the significant risk of misclassification of dysplasia all tend to undermine the effectiveness of current management, in particular endoscopic surveillance programs, to prevent or improve the outcomes of patients with oesophageal adenocarcinoma. The ongoing increase in Barrett's oesophagus incidence and consequent growth of the surveillance population, together with the associated discomfort and costs of endoscopic surveillance, demand improved techniques for accurately determining individual risk of oesophageal adenocarcinoma. More accurate techniques are needed to run efficient surveillance programmes in the coming decades. In this review, we will discuss the current knowledge on the epidemiology of Barrett's oesophagus and the challenging epidemiological dilemmas that need to be addressed when assessing the current screening and surveillance strategies.

Keywords

Barrett's oesophagus; Endoscopic surveillance; Oesophageal adenocarcinoma; Epidemiology; Prevention

Introduction

In 1952 the incidence of oesophageal adenocarcinoma was low enough that an oesophageal adenocarcinoma (OAC) in Barrett's oesophagus (BO) merited a case report.(1) OAC has

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now become the fifth leading cause of cancer-related death in males worldwide,(2) with its incidence continuing to rise inexorably in the western world.(3, 4)

The dismal prognosis of OAC has focused interest on BO, its precursor lesion and a very common condition with population series demonstrating a prevalence of up to 42.000 cases (?- what does 42.000 refer to. The estimates I have seen are 2–25% of the population in western countries).(5, 6) BO is defined by replacement of oesophageal squamous epithelium by columnar epithelium with intestinal metaplasia as a consequence of gastro-oesophageal reflux disease (GORD).(7) The cascade of GORD to BO and ultimately OAC offers attractive targets for screening and surveillance. These interventions aim to decrease mortality and improve survival related to OAC by early detection and treatment of either dysplastic BO tissue or early cancer. Endoscopic surveillance of BO has been recommended in various guidelines by different gastroenterological societies and as such has been widely implemented.(8–12) However, as current evidence for either improved survival or cost-effectiveness is equivocal at best, the efficacy of BO surveillance remains the subject of heated debate.(ref's, Sharma, 2012) This uncertainty also limits the basis for population BO screening.

In view of new epidemiological data that have become available since the development of surveillance guidelines, reconsideration of effective preventive strategies for BO patients seems justified. This review will provide an overview of our current knowledge on the epidemiology of BO and the challenging epidemiological dilemmas that need to be addressed when assessing screening and surveillance strategies and the strategies that will be needed for effective screening and surveillance programs in the future.

Epidemiology of Barrett's oesophagus

The epidemiology of BO is especially complicated because the majority of affected individuals are asymptomatic and remain undiagnosed.(13) Those patients who come to medical attention are likely to represent a subpopulation that may very well differ from those who remain undiagnosed. Published epidemiological data can therefore only be an approximation of the true prevalence of BO.

Prevalence of Barrett's oesophagus in the general population—Most prevalence data have been derived from BO diagnoses made during oesophago-gastro-duodenoscopy (OGD) performed for dyspeptic symptoms, however, more recently, BO prevalence has been studied in unselected populations. More than 20 years ago, an autopsy study found BO in seven of 733 unselected cases (0.95%).(14) Recently, an overall BO prevalence of 6.8% was found in a cohort of 961 patients undergoing colonoscopy that were offered an additional OGD. Short-segment BO (SSBO) was relatively common in persons aged 40 years or older (5.5%), irrespective of heartburn history.(15) A similar colonoscopy based study, limited to 300 subjects over age 65, found long segment BO (LSBO) in 4% and SSBO in 15%, with a clear male predominance, and notably, without a significant relation with reflux symptoms. (16)

So far, three population-based studies have addressed the prevalence of BO in the general population. In the first, Ronkainen *et al.* performed upper endoscopy in a random sample of

1,000 Swedish adults.(17) BO was found in 1.6%; long segment in 0.5% and short segment in 1.1%. The second examined 1,033 Italian adults with similar characteristics to the general Italian population.(18) BO was found in 1.3%; 0.2% had LSBO, whereas 1.1% had SSBO. The third endoscopic survey was performed in China.(19) (Did these studies diagnose BO by endoscopy alone, or was histology required as well?) Endoscopically suspected BO was present in 1.9% of 1030 subjects, with only 26% of them having a maximum extent of metaplasia 3 cm or greater. These estimates indicate that approximately 0.5 – 1.5% of Western populations would need to be offered regular endoscopic surveillance, according to current guidelines, if BO surveillance programs are to be implemented.

Age, sex and ethnic distribution of Barrett's oesophagus—A British endoscopy study reported a 7% annual increase in BO prevalence for both sexes. For men this increase started at age 20, however, in women it was delayed until age 40, resulting in a 20-year age shift and an overall 2:1 male predominance among BO cases.(20) A large Dutch general practice registry confirmed the parallel age-specific increases in BO, with a similar 20-year age shift between men and women.(21) The Northern Ireland Barrett's oesophagus registry (NIBR) which included over 9000 patients with BO, also noted significantly fewer females than males diagnosed with BO in the age group of 16 to 40 years.(22) This delayed development of BO is consistent with the a 17-year delay in female OAC incidence, leading to an overall 3.5:1 male predominance, presumably as result of women acquiring BO at an age when they die from other causes before developing OAC.(23, 24) This observation may relate to an endogenous protective effect related to sex-specific hormone production observed in premenopausal women, most likely oestrogen, which is known for its anti-inflammatory effects in certain tissues.(11) The relationship between the prevalence of reflux oesophagitis and obesity in women suggests that this hormonal protection for women may disappear with their tendency to gain weight during perimenopause.(25) The interaction between oestrogen and obesity in this respect needs further study.

Apart from these gender-related differences in BO epidemiology, there are also marked ethnic differences. A report from the United States (U.S.) based on SEER data noted far higher OAC rates in Caucasian white males than in black American males, with female rates far lower for both ethnic groups.(3, 26) In the U.K. a higher BO prevalence in white Caucasians compared to Asians was reported.(27) Data on the prevalence in Hispanics are contradictory, with some studies showing a similar prevalence to that in Caucasians,(28) and other studies showing a lower prevalence.(29, 30)

Increasing incidence of Barrett's oesophagus in the general population—The dramatic increase in the incidence of OAC over the past decades is thought to have been preceded by a similar steep increase in incidence of BO. Methodological problems have, however, confused the measurement of actual BO incidences.(31–33) Some of the reported increases in newly diagnoses are most likely a result of more widespread use of endoscopy, increased awareness of BO among endoscopists, and higher oesophageal biopsy rates. However, a 93% increase in BO incidence between 1993 and 2005 was recently published from the NIBR, where the potential confounding by number of endoscopies was avoided by counting the number of BO cases per 100 endoscopies.(34) A similar Dutch study also

reported an increase in BO incidence irrespective of numbers of performed OGDs. Importantly, the increased incidence was most pronounced among males under 60 years of age, suggesting a birth cohort effect, which might be related to increasing affluence after World War II.(35) Similar cohort phenomena in OAC incidence were reported using U.S. SEER-data,(36) and more recently in another study from the Netherlands.(37)

Explanations for the increasing BO incidence—One popular explanation for the increasing incidence of BO in Western countries is the decreasing prevalence of gastric colonisation with *Helicobacter pylori*.(38) A population-based study provided evidence that absence of *H. pylori* colonisation was associated with BO.(39) The suggested mechanisms for the inverse association include decreased acid production through gastric atrophy by *H. pylori* infection(40, 41) and enhancement of gastric emptying, especially in younger persons.(42) A parallel between the aforementioned birth cohort effect in BO incidence, and that of the prevalence of *H. pylori* was also reported.(43, 44). The considerably lower OAC rates in countries with a high prevalence of *H. pylori* also provide support for this hypothesis.(45–47) However, *H. pylori* infestation can also augment acid production. The OAC incidence of Swedish in-patients treated for duodenal ulcer during the 1960's considerably exceeded that of their contemporary gastric ulcer patients and the general Swedish population.(48) Furthermore, the *H. pylori* hypothesis fails to explain the male predominance and ethnic differences in both BO and OAC incidence.

Therefore an alternative hypothesis to explain the increasing prevalence of BO and OAC that is based on the prevalence of obesity has been proposed and is gaining popularity. This hypothesis proposes that the mounting prevalence of obesity, in particular visceral obesity, is responsible for the rising incidences of BO and OAC. A recent review, including a number of prospective cohort studies, found abundant evidence for obesity as the driving force behind the rising OAC rates.(49) Obesity has been associated with a significant 1.5- to 2-fold increase in the risk of GORD symptoms and erosive oesophagitis, and a 2- to 2.5-fold increase in the risk of OAC.(50) Possible mechanisms mediating this association include increased intragastric pressure and gastro-oesophageal pressure gradient,(51) more frequent transient relaxations of the lower oesophageal sphincter,(52) and increased oesophageal acid exposure.(53)

Two large case–control studies from the U.S. have reported that in particular abdominal circumference (ie waist-hip ratio), but not body mass index (BMI), was an independent risk factor of BO. (54, 55) A study among veterans based on CT scans showed that visceral adipose tissue (VAT) but not BMI was independently associated with BO.(56) The suggested mechanism could relate to the induction of a systemic pro-tumorigenic inflammatory state as a result of adipocytokines and pro-coagulant factors released by adipocytes in abdominal VAT. A high prevalence of metabolic syndrome in BO, especially in LSBO, with increased cytokine and fasting insulin levels, as compared to SSBO patients has been found.(57) In addition, VAT has also been strongly associated with increased serum levels of interleukin 6 (IL-6), tumour necrosis factor α (TNF-α), and C-reactive protein,(58) as well as with leptin, which may stimulate cell proliferation and inhibit apoptosis in Barrett's-derived OAC cells. (59).

Visceral obesity may well help to further explain several epidemiological features of BO such as the sex and ethnic differences. A much stronger association between increasing BMI and GORD symptoms has been observed among whites than among black subjects and Asians,(60) while white males have more VAT than black males.(61) Another U.S. study revealed that, at the same age and level of adiposity, black men and women had less VAT than white men and women, these differences were greater in men than in women.(62) VAT was also higher in white than in black postmenopausal women, although the latter had higher levels of subcutaneous fat.(63) After menopause, VAT has been shown to increase in European-American, but not in African-American women.(64) However, larger amounts of visceral adipose tissue were observed in Asian Americans than in white subjects.(65) Genome wide studies have identified a number of genetic loci involved in abdominal fat distribution, BMI and obesity. (66, 67) Further studies between the association of BO and these genetic loci to confirm these observations are now indicated.

Based on these correlations, it is plausible to assume that the steadily increasing prevalence of obesity,(68, 69) in particular visceral obesity, in many populations will drive an increase in incidence of BO and OAC.

Cancer risk in patients with Barrett's oesophagus

Accurate estimates of the annual incidence of OAC and high-grade dysplasia (HGD) among patients with BO have been difficult to obtain, since studies have shown considerable variation in incidence rates. Published data predominantly have come from small cohort studies with relatively short follow-up, and mostly from referral centers, which likely have ascertainment biases that will show a higher cancer incidence than may be observed in larger population-based surveillance studies. Consequently, in light of these issues, it is not surprising that evidence of publication bias in surveillance studies favouring publication of small studies with high cancer incidence rates has been reported.(70)

Meta-analyses on cancer risk—Currently, seven systematic reviews have been published on the cancer risk in patients with BO.(70–76) The pooled estimates for the annual OAC incidence among BO patients in these reviews varied between 0.3% and 0.6%, and between 0.9% and 1.0% for the combined incidence of HGD and OAC (Table 1).

It should be noted that two reports failed to exclude early incident cancers (detection within one year after baseline diagnosis of BO),(70, 71) and three included cancers occurring in patients with HGD at baseline,(70–72) thereby inflating OAC risk of patients with uncomplicated BO. Although geographic differences in the population incidence of OAC exist,(26, 77) none of these reviews could confirm a significant geographic variation in BO-associated cancer risk.(78)

In order to obtain more accurate estimates of the risk of OAC in BO patients, analysis of the data derived from high-quality studies (large study size, robust definition of BO) has been preformed and has tended to show a lower cancer risk. Perusal of a funnel plot of incidence rates of OAC against the number of patient years revealed that the annual OAC incidence rates in BO cohorts with less than 2000 patient years widely ranged between 0 to 3.55%, and fell to 0.07 – 0.82% in cohorts with more than 2000 patient years of follow-up.(74) The

reliability of OAC incidence rates thus appears to depend on the size of the cohort and duration of follow-up. Besides the obvious higher chance of random deviation from the norm in small studies, there are a number of potential confounders that can strongly influence outcomes such as variations between cohorts in the male-female ratios, and age at BO ascertainment. A less obvious confounder is the proportion of the cohort lost to follow up, with the resultant loss of both follow-up years and OAC ascertainment, resulting in unreliable high OAC incidence rates.(79)

Population-based cohort studies—Recently, three population-based BO follow-up studies were published in which national cancer registries provided complete ascertainment of the OAC incidence(6, 80). Inclusion in the BO cohorts was based on national histopathology registries, while inclusion in the third study was based on an endoscopy registry.(81) (Table 2) The design of these studies strongly reduced selection bias, which has been a particular limitation of previous cohort studies. The first and largest study consisted of 42,207 patients entered in a Dutch nationwide histopathology registry between 1991 and 2006 with a first diagnosis of BO with intestinal metaplasia and including either no concurrent dysplasia or at most low-grade dysplasia.(6) Subsequent histological events were monitored until November 2007, or a diagnosis of OAC or HGD was made. The number of patient years for the remainder of the cohort was estimated from survival data from the general Dutch population. For BO patients undergoing endoscopic follow-up after baseline diagnosis, the annual OAC risk was 0.4%; however, when cancer risk was analyzed for all BO patients, regardless of whether any follow-up was performed, the annual OAC risk dropped to 0.14%, with 0.19% in males and 0.08% in females.

The second study comprised 11,028 BO patients with intestinal metaplasia, with or without low-grade dysplasia, enrolled in the Danish Pathology Registry from 1992 through 2009. (80) The civil registration number assigned to all Danes enabled data linkage of all medical registries and dates of emigration or death. After again eliminating all OAC cases occurring in the first year after index BO diagnosis, the authors found an annual OAC risk of 0.12% for the entire cohort, 0.15% for males and 0.05% for females.

The last study was the third update of the NIBR BO cohort, comprising every adult diagnosed with BO in Northern Ireland between 1993 and 2005. (81) The cohort includes 8,522 BO patients, with or without intestinal metaplasia, followed until the end of 2008. The ascertainment of OAC was achieved by matching NIBR registry data with that of the Northern Ireland Cancer Registry. Besides including BO without intestinal metaplasia at index biopsy, the cohort differed from the two previous studies in that for some patients endoscopic data were available. An annual cancer risk of 0.13% for the entire cohort was found; 0.17% for males and 0.08% for females. Although data on length of BO and the presence of intestinal metaplasia were incomplete, it proved possible to show that OAC risk was significantly increased to 0.27% in the presence of intestinal metaplasia at index endoscopy, however no effect of the length of the BO segment was observed.

Some limitations of these studies warrant consideration. First, all three studies included the incidence of HGD as an outcome. As these were observational cohorts and HGD is often asymptomatic, the ascertainment of HGD was far inferior to that of OAC and consequently

considerably underestimated the incidence of HGD. Second, both sampling error and misclassification of dysplasia status may have affected the published results. Thirdly, some patients with intestinal metaplasia of the cardia could have been misclassified as having BO, as endoscopic data were not provided. Nevertheless, the study size, population-basis, low 'loss to follow up' rates, and high OAC ascertainment though linkage of histology and cancer registries are major advantages of these studies. In addition, the finding of remarkably similar absolute annual risks of 0.12% to 0.14% provides support that these studies are reporting accurate incidence data. Consequently, these studies have redefined the cancer risk of BO that is relevant to clinical practice and have set new standards for assessing OAC risk in BO.

Risk of mortality in patients with Barrett's oesophagus—Whether patients with BO have an increased mortality risk from causes either related or unrelated to OAC compared to the general population remains controversial.(31, 82–88) In studies reporting an excess mortality, this was primarily due to extra-oesophageal diseases such as pneumonia and in particular cardiovascular disease. It may well be that patients with pre-existing illness are more likely to have endoscopy and to have BO found than other members of the population.(31) In addition, increased mortality due to cardiovascular disease in BO may result from a shared association with obesity.

Screening for Barrett's oesophagus

The high prevalence of BO and its expected mounting incidence in the general population, which heralds a further increase in OAC incidence, can be seen as arguments for targeted population screening for BO. Based on the epidemiological data described above, this approach would seem to be a plausible and necessary step to ultimately decrease OAC-related mortality. In order to achieve this goal, subjects at risk of BO would need to be identified, and either treated or monitored under surveillance or both. However, for these approaches to have optimal efficacy, methods for the accurated assessement of an individual's cancer risk are needed.

Predictors of Barrett's oesophagus—BO is associated with increasing age, male gender, Caucasian race and visceral obesity,(74, 89, 90) but symptomatic GORD remains its best known risk factor. While the severity of reflux symptoms fails to distinguish between reflux oesophagitis and BO,(91) a long duration of reflux symptoms seems a better indicator of the presence of BO, (92, 93). In a community-based study, as compared to patients with GORD symptoms for less than 1 year, the relative risk of BO was respectively 3.0 and 6.4 for patients with reflux symptoms for 1–5 years and > 10 years.(94) Cigarette smoking is also a modest risk factor for BO.(95) A recent analysis from five case-control studies reported adjusted odds ratios in the range of 1.5 to 2; the association strengthened with increased exposure to smoking until approximately 20 pack-years.(96) Currently there is no evidence that alcohol intake increases the risk of BO.(97, 98) Two recent studies have even suggested an inverse association between BO and wine consumption.(99, 100) Families with BO and OAC in multiple relatives over successive generations have been reported, suggesting a heritable component to BO and OAC.(101–103) One study showed that familial BO was present in 30 (7.3%) of 411 probands with either LSBO, OAC or adenocarcinoma

of the gastro-oesophageal junction, comprising 17 of 276 (6.2%) with BO, 11 of 116 (9.5%) with OAC, and 2 of 21 (9.5%) with adenocarcinoma of the gastro-oesophageal junction.(104) Another study reported a 24% BO prevalence among first-degree members of BO index cases.(105) A segregation analysis involving data on 881 singly ascertained pedigrees provided epidemiologic evidence in support of one or more rare autosomally inherited dominant susceptibility allele(s) in BO families, and, hence, motivated linkage analyses.(106) Germline mutations in the *MSR1, ASCC1*, and *CTHRC1* genes have been associated with the presence of BO and OAC(107), and a recent GWAS study with 5.986 BO cases and 12,825 controls in the replication stage found that genetic variants at two loci were associated with BO risk; one located at chromosome 6p21 within the major histocompatibility complex, and one on chromosome 16q24 for which the closest protein-coding gene was FOXF1, which is a transcription factor involved in oesophageal development and structure.(108)

Current guidelines for screening for Barrett's oesophagus—Currently the American Gastroenterological Association (AGA) position statement on the management of BO recommends enrolling patients with multiple risk factors associated with oesophageal adenocarcinoma (in particular 50 years of age or older, male gender, white race, chronic GORD symptoms, and an elevated body mass index) in screening programs, although this was classified as a weak recommendation with moderate-quality evidence.(10) The committee recommended against screening all patients with GORD; this was classified as a strong recommendation with low-quality evidence. This statement corresponds to the American Society for Gastrointestinal Endoscopy (ASGE) guidelines.(12) The committee remarked that screening remains controversial in the absence of any documented impact on mortality from cancer. The British Society of Gastroenterology (BSG) and the French Society of Digestive Endoscopy (SFED) recommend against screening and do not make exceptions for any subgroups of patients.(8, 11) In the absence of randomised controlled trials of endoscopic screening, some cost-effectiveness modelling studies have indicated that screening programmes may be cost-effective,(57, 58) whereas other modelling studies have not.(59)

Dilemmas in screening for Barrett's oesophagus (Box 1)—One major dilemma that diminishes the utility of screening is that a significant proportion of BO patients lack reflux symptoms. In population-based studies of the prevalence of BO, over 45% of identified BO patients did not report symptoms of GORD.(17, 18) In addition, even in patients with OAC, approximately 40% have no GORD history prior to diagnosis.(109) Therefore, symptomatic GORD as a selection criterion for endoscopic screening is likely to exclude half the BO population. In fact, even if one accepts GORD as an entry criterion, a second dilemma is that the at-risk population is very large, as GORD symptoms are ubiquitous in the general population, with a prevalence of 15–20% in the Western World, and an incidence of approximately 5 per 1000 person years.(110) Implementation of a screening program for BO based on GORD symptoms would consequently create a huge burden on the health care system, which is difficult to justify at this time given the paucity of data demonstrating a benefit of BO screening programs on health outcomes. Another question that would need to be addressed in a BO screening program is what age should

screening be initiated. The yield of BO will be higher in older populations, however, in view of the long incubation period between the onset of BO and OAC, the majority of the elderly BO subjects are unlikely to develop OAC. Therefore, screening at age 40 would probably identify a higher proportion of BO patients who will ultimately develop OAC. However, these subjects would then be committd to decades of endoscopic surveillance with limited benefit per screening session given the low annual cancer risk.

There are also substantial problems with the execution of various facets of endoscopic screening and surveillance programs, such as false BO diagnosis through biopsies of the gastric cardia, resulting in unnecessary patient anxiety, unnecessary follow-up examinations, and, in the U.S., increased expense and difficulty in obtaining life and other insurance.(111) In addition, OGD is relatively expensive,(112) and carries a, albeit small, risk of complications, which becomes important when applied to large populations in a screening setting.(113, 114) Furthermore, the procedure is obviously burdensome to many patients, (115) especially since patients diagnosed with BO may overestimate their cancer risk, contributing to a decreased quality of life.(116) These limitations all favor restricting the use of endoscopic procedures for BO screening in large, population based screening programmes.

Potential new minimally-invasive screening modalities—Less invasive technology may solve the latter problem. A recent study offering unsedated transnasal endoscopy and video capsule endoscopy as alternatives to sedated endoscopy demonstrated positive responses of 50%, 59% and 38% respectively to these three techniques, which suggests that the non-invasive methods are preferable to patients.(117) Ultra-thin video endoscopes can easily be passed transorally or transnasally, providing an efficient, cost-effective alternative to standard sedated endoscopy.(118) However, a recent study failed to show a large increase in the number of primary care referrals for BO screening with unsedated ultrathin OGD. (119) As patients generally desire a procedure totally lacking any potential discomfort, unsedated OGD has not been accepted for wide scale use.

Oesophageal capsule endoscopy (OCE) offers a method of visualizing the oesophagus without the discomfort and risks of OGD. Initial pilot studies have demonstrated a high diagnostic yield of BO, a high patient preference, and no safety problems.(120, 121) However, a meta-analysis of nine studies on the diagnostic accuracy of OCE for BO have reported a relatively low sensitivity (77%) and specificity (86%) for detecting BO.(122) These suboptimal test performances, together with the current the high cost of capsules and the inability to biopsy any detected BO are obvious disadvantages to OCE and preclude OCE as a screening test for BO in GORD patients.

Recently a non-endoscopic screening test with the ability of tissue sampling has been developed. This non-endoscopic test, the Cytosponge test, is based on an ingestible oesophageal sampling device that allows cytology samples to be retrieved from the oesophagus that can then be used in immunohistochemical assays of trefoil factor 3. This method may be the most promising alternative to endoscopic screening. It has an acceptable sensitivity and specificity for BO (73% and 94%, respectively), is easily applicable in primary care, and well tolerated by most patients.(123, 124) Furthermore, the binary scoring

for trefoil factor 3 makes the test amenable to automation. A recent cost-effectiveness model showed that screening based on the Cytosponge assay in 50-year-old men with symptoms of GORD followed by treatment of patients with dysplasia or intramucosal cancer is cost effective and would reduce mortality from OAC compared with no screening.(125) Further validation of the Cytosponge test in different communities is required to assess its potential role in future BO screening. The most ideal screening test, however, would be based on the use of serum biomarkers, which are under development and which may be available in the future.

Surveillance of patients with Barrett's oesophagus

Once BO is diagnosed, patients are offered endoscopic surveillance, in order to detect high-risk BO (e.g. BO with high-grade dysplasia) or early-stage cancers suitable for curative treatment. Thus, several factors need to be considered in individual patients before starting endoscopic surveillance, such as age, comorbidity, the patient's understanding of limitations of endoscopic surveillance, and the willingness of the patient to adhere to be compliant with the endoscopy based surveillance program.

Current guidelines for endoscopic surveillance—The majority of societal guidelines base the interval of surveillance endoscopy solely on the histological evaluation of biopsy samples, but usually not take other factors into account, such as for example age, gender, and BO segment length (Table 3). For BO patients without dysplasia, current guidelines by the ACG and ASGE recommend surveillance endoscopy at three year intervals. For patients with LGD, annual surveillance endoscopy is recommended, and for those with HGD who receive no invasive therapy, intensive endoscopic surveillance exams every three months is recommended.(9) The recent AGA medical position statement on the management of BO recommends intervals between 3 and 5 years for NDBO.(10) According to guidelines from the BSG, patients with NDBO should undergo surveillance endoscopy every two years.(126) An important difference between the BSG and the U.S. guidelines is that the presence of intestinal metaplasia is not a requirement for the diagnosis of BO by the BSG, the rationale being that sampling errors at the initial endoscopy may miss areas of intestinal metaplasia, and that BO can usually be demonstrated by increasing the number of biopsies.(127, 128) The SFED (French Society of Gastrointestinal Endoscopy) is the only society that correlates the surveillance interval for patients with no dysplasia to the length of the BO segment; in those with SSBO surveillance endoscopy should be performed every five years, in those with a segment length of 3–6 cm, every three years and in those with segments longer than 6 cm, every 2 years.(11)

Dilemmas in endoscopic surveillance of Barrett's oesofagus—Although surveillance endoscopy is intuitively rational and endorsed by international gastroenterological societies, the data supporting many aspects of the recommended strategies are based on equivocal data. Consequently most recommendations are classified as weak. More importantly, there are no prospective randomised controlled trials unequivocally demonstrating a beneficial effect of endoscopic surveillance on OAC mortality. Retrospective studies have shown that patients with OAC were more likely to have their cancer detected at an earlier stage when they had previously been in a surveillance program

compared to those patients not under surveillance.(129) Furthermore, early recognition of HGD or cancer has been associated with an improved survival from OAC.(130) However, results of non-randomised comparisons between surveillance and non-surveillance detected cancers are hindered by a variety of factors including lead-time and length bias, which falsely associate surveillance programs with improved outcomes.(131)

One further problem with surveillance is that, although the vast majority of OAC cases arise in the setting of BO, only a small proportion of BO patients will eventually develop OAC,(6, 132) and even less will eventually die from OAC. In a cohort study from the Netherlands, only 5.6% of total mortality among BO patients was related to OAC.(82) Another observational study following a cohort of 409 BO patients for 10 years showed that only four (1.0%) of them died as a result of OAC.(79) Moreover, an estimated 95% of patients with a new diagnosis of OAC do not have a previous diagnosis of BO,(13) suggesting that for the general population, BO surveillance programs will only have a modest effect on OAC mortality.

Several authors have used mathematical models to explore the cost-effectiveness of BO surveillance.(133–135) U.S. researchers concluded that, for a cancer risk of 0.5% per annum, surveillance every 4 years was indicated, but if the annual risk was 0.4%, surveillance every 5 years was the only viable cost-effective strategy.(135) Others reported that screening 50-year-old men with GORD to detect adenocarcinoma was probably cost-effective when subsequent surveillance was limited to BO patients with dysplasia ($10.440 per quality adjusted life year (QALY)). Screening was, however, far too expensive when surveillance was also performed in NDBO patients, even at 5-yearly intervals (additional $596.000 per QALY).(134) A British cost-efficacy study reported that at an annual cancer risk of 0.5%, BO surveillance conferred less benefit and more costs than no surveillance at all, irrespective of the surveillance interval used.(133) The outcomes of all these modeling studies were strongly influenced by predefined parameters, the most critical of which was the annual incidence of OAC among BO cases, with most assuming 0.4–0.5%, which is the incidence still employed in current surveillance guidelines.(9) Consequently, the observed 0.12–0.14% incidence from the recent population studies will only further provide support against the cost-effectiveness of surveillance.

The execution of surveillance is also beset by technical problems. As dysplasia in Barrett’s mucosa is often patchy, its diagnosis is subject to sampling error when biopsy based sampling methods are used for its detection.(136) For example, in a series of patients undergoing oesophagectomy for HGD without apparent tumour mass, invasive cancer was found in 30–40% of the resected specimens.(137) In addition, in a Danish study of newly diagnosed BO patients, more than two thirds of all OACs were diagnosed during the first year of follow-up, indicating sampling error at the index biopsy.(80) Extensive biopsy sampling, known as the Seattle biopsy protocol, has been recommended for decreasing sampling error, but is unable to eliminate the problem entirely, because even if it is properly performed, only 4–6% of the BO area can be sampled.(138) Although the protocol has been associated with increased detection of dysplasia and invasive cancer,(139) in daily practice adherence to such a rigorous endoscopic surveillance protocol seems to be poor and compliance is inversely associated with the length of the BO segment. In a Dutch

retrospective study of endoscopic and pathology reports, adherence to the Seattle protocol was as low as 30%, in particular among BO patients with segments of 10 to 15 cm in length.(140) A similar U.S. study reported an overall adherence of only 51%, with evidence that failure to protocol adherence was associated with decreased rates of dysplasia detection.(141) These findings suggest that for those BO patients at highest risk of development of OAC, adherence appears to be the poorest. Advanced endoscopic techniques, such as chromoendoscopy, narrow-band imaging (NBI) and autofluorescence endoscopy, which are intended to enhance the detection of dysplastic areas for biopsy sampling, are promising,(142) although they have not consistently been shown to increase neoplasia detection as compared to high-resolution white light endoscopy. A recent randomised controlled trial showed that use of NBI targeted biopsies and the current standard of random four quadrant biopsies diagnosed similar proportions of patients with BO, although NBI could achieve this with significantly fewer biopsies, suggesting improved efficiency and consequent cost reduction.(143) However, as the study was limited to three tertiary BO referral centers, these results cannot be directly extended to non-tertiary centers.

The substantial disagreement among pathologists in assessing the presence and grade of dysplasia has also raised concerns about the use of surveillance programs that depend on accurate determinations of dysplasia in BO. The interobserver agreement in differentiating HGD from intramucosal cancer is only fair,(144) while the interobserver agreement for the distinction between no dysplasia (ND) and low-grade dysplasia (LGD) is poor,(145, 146). A retrospective study of the natural history of LGD in a community-based cohort of BO patients demonstrated that following review by two expert pathologists, 85% of patients with an initial diagnosis of LGD could be downstaged to ND or indefinite for dysplasia, while those with a consensus diagnosis of LGD had significant higher rates of malignant progression than patients downstaged to ND.(147) These findings indicate that a new diagnosis of low-grade dysplasia in particular should always undergo expert pathology review. Furthermore, the diagnosis of dysplasia varies between consecutive screening biopsies, which may be a result of sampling error, but may also indicate the inconsistent nature of this risk marker. It remains unclear whether dysplasia can regress over time. Misclassification of the presence and grade of dysplasia may lead to unnecessary follow-up endoscopies in case of overdiagnosis, or to possibly insufficient follow-up exams with inappropriate surveillance intervals in the case of underdiagnosis.

Risk stratification in patients with Barrett's oesophagus

The prolonged interval between BO onset and OAC incidence implies that the rational management of individual patients will require the ability to establish in any given BO patient an accurate assessment of risk for developing OAC and the approximate time to progression. To attain this goal, a prediction model, preferably based on demographic, environmental, endoscopic as well as histological markers, is obviously needed. A recent systematic review by Prassad *et al.* described the current state of knowledge on predictors of progression in BO in detail.(148) In the following paragraph, the current state of predictive factors for OAC is summarized.

Demographic and environmental risk factors—Male gender remains the most robust demographic factor predictive of OAC development. Population-based studies as well as systematic reviews have shown a much higher OAC incidence in males with BO than in females with BO.(6, 73, 80) This finding is consistent with the strong male predominance in patients with OAC.(26, 149) The role of age on the progression in BO is, however, less clear. Several studies have shown that increasing age is an independent predictor of OAC development,(150) with the highest incidence of OAC among BO patients older than 70 years of age,(80) although other large cohorts could not confirm this.(151, 152) A retrospective study from the Cleveland Clinic BO registry did not show different rates of progression between BO patients younger and those older than 50 years.(153) However, in a prospective observational cohort study from our centre, patients with a diagnosis of BO as long as 10 or more years prior to inclusion had a 3-fold increased risk to develop HGD or OAC as compared to patients with a shorter known duration of BO diagnosis.(154) Assuming the existence of an incubation period of three or four decades between BO onset and OAC development,(155) and that the prevalence of BO increases with age, the smaller number of patients acquiring BO around the fourth decade are far more likely to survive long enough to develop OAC as compared to the great majority acquiring BO in the fifth and sixth decades. Consequently, the generally unknown age of BO onset would be far more relevant to prognosis than age itself, if this could be determined.

Malignant progression in BO has also been associated with both an increased BMI at young age, (156) and an increased waist-to-hip ratio, the latter being associated with an increased proliferation rate in BO as indicated by an increased percentage of S-phase cells.(157) In addition, increased waist-to-hip ratio, a surrogate marker of VAT distribution, but not BMI, was shown to be related to the risk of aneuploidy, 17p LOH and 9p LOH, (158), confirming VAT as a potential predictor of neoplastic progression.

Smoking has in some studies been suggested as an additional risk factor for progression to OAC, (156, 159, 160) while other investigators did not confirm this.(152, 154, 161)

Endoscopic risk factors—Multiple prospective studies have found that length of the BO segment is a risk factor for development of OAC.(162–165) A recent prospective cohort study of 713 BO patients found that each centimeter increase in BO length was associated with an 11% increase in the risk of developing HGD or OAC.(161) The increased risk probably reflects a larger surface area at risk of neoplastic progression. The presence of baseline dysplasia can be an important confounder of this association between BO length and OAC incidence. In a large prospective cohort study, after adjustment for histology at study entry, segment length was not a significant predictor of progression.(166) However, a recent meta-analysis on cancer risk in NDBO patients, reported an overall OAC risk of 0.33% (95% CI 0.28% to 0.38%), but only 0.19% for SSBO patients without dysplasia.(76) It further remains to be clarified whether there is a specific length at which the risk of neoplastic progression increases significantly.

In patients with HGD nodularity or visible endoscopic lesions, there is an increased risk of progression to OAC.(167, 168). However, visible lesions have rarely been studied in patients without HGD, hence, in many patients, nodularity may rather indicate the prevalence of

concurrent HGD or OAC rather than a risk of future progression. This has also been confirmed in oesophagectomy specimens where nodularity in HGD often represented undetected EAC.(169, 170)

Both the presence and size of a hiatal hernia have been associated with increased OAC risk,(161, 162) although these are probably merely surrogate markers for the severity of GORD. Oesophagitis has been reported to predict a 3.5 times higher risk of developing HGD/OAC in BO patient compared to those without.(152) The underlying inflammation in oesophagitis is believed to increase the risk of mutations leading to HGD and OAC.(171).

Dysplasia and role of biomarkers—Currently, the grade of dysplasia is the most widely used and accepted marker for risk stratification in BO, but its value may be diminished by interobserver disagreement and sampling error. A correlation between the extent of dysplasia to the risk of progression to OAC has been sought. In patients with HGD, this was found to predict risk of progression to OAC (14% at 3 years in focal HGD vs. 56% in diffuse HGD).(167) However, this finding was not confirmed by subsequent studies.(172) Recently an association was found between the extent of LGD (measured by the total number and fraction of dysplastic crypts) and the risk of progression to OAC, but not to HGD.(173)

There have been a number of attempts to identify biomarkers supporting or even replacing histology in dysplasia classification. Immunostaining for alpha-methylacyl-Coaracemase (AMACR), and for a panel of biomarkers including beta-catenin, cyclin D1, and p53 were proposed to distinguish dysplasia from reactive changes and among grades of dysplasia,(174–176) However, the utility of such panels was shown to be limited by significant interpatient and intrapatient variations in gene expression levels.(177) A number of biomarkers other than the histologic finding of dysplasia have been proposed to predict which patients are at greatest risk of developing OAC. In fact, the published literature has reported on more than 60 biomarkers for this purpose. DNA content abnormalities such as aneuploidy within the Barrett’s mucosa have shown some promise.(178, 179) Other molecular markers showing correlations with BO progression to OAC are tumor suppressor loci (p53 LOH), epigenetic markers (p16 methylation), cell cycle markers (cyclin-D1) and proliferative markers such as Ki67.(180) Unfortunately, no single marker fulfilling clinical requirements has yet been identified and validated. Panels of biomarkers such as gene methylation-based biomarker panels (181, 182) or the Reid panel, which combine LOH at various loci and DNA content abnormalities,(178, 179, 183) appear to provide the most accurate predictors of progression. Unfortunately, they are currently still far too expensive for application in routine clinical use, and the necessary technical expertise is not universally available for wide-scale deployment of these methods. Therefore, replacing dysplasia with the routine use of biomarkers can not be recommended at this time. However, biomarkers may well hold out the best prospects for BO risk stratification.

Management of patients with non-dysplastic Barrett’s oesophagus revisited

Endoscopic surveillance of BO patients without dysplasia remains the subject of debate, even more so since the publication of population-based studies that demonstrate a low OAC

risk in BO patients. These new estimates have important implications for the clinical management of BO patients. Firstly, the downgraded risk estimates of cancer in NDBO provide little support for the effectiveness of current surveillance at 3–5 years intervals. A recent meta-analysis of cost-effectiveness studies on endoscopic surveillance of NDBO, which was based on older and probably overestimated cancer risk estimates, already concluded that current surveillance strategies are unlikely to be cost-effective.(184) Although the value of dysplasia as a marker for risk stratification is hampered by interobserver disagreement and sampling error, all recent population-based cohort studies show that low-grade dysplasia at index biopsy was associated with a considerably heightened OAC risk, this in spite of the fact that most cases will not have been diagnosed by specialist pathologists. This raises the question whether long-term surveillance can be omitted in some BO patients when absence of dysplasia has been confirmed repeatedly. Given the fact that a large proportion of OAC seems to occur within a year from BO diagnosis, it remains of paramount importance to perform an adequate endoscopic inspection at initial diagnosis, combined with obtaining a sufficient number of biopsy specimens to confidently assess for dysplasia. A subsequent follow-up endoscopy one year after diagnosis, especially in LSBO, should be performed, in order to be more confident of a true absence of neoplastic or dysplastic histology. Although current epidemiological risk factors for cancer progression do not discriminate perfectly between low-risk and high-risk patients, they still strongly suggest that in particular white female SSBO patients without dysplasia at index diagnosis are the least likely to benefit from surveillance. In male SSBO patients without dysplasia a stopping rule for surveillance should be implemented after 2 endoscopies without dysplasia in non-targeted biopsy sampling. In LSBO patients, it may be reasonable to extend further surveillance intervals from the currently proposed 3 years to 5 years when absence of dysplasia has been confirmed, or even longer when no additional risk factors such as smoking and obesity are present.

A second important implication is that the new cancer risk estimates advocate against the increasing use of ablation therapy in NDBO patients. Given the low rate of cancer progression, the benefit of such intervention, even if leading to complete ablation, is unclear. A cost-utility analysis by Inadomi *et al.* suggested that ablation therapy of NDBO could be the preferred management strategy if the procedure eliminates the need for long-term endoscopic surveillance.(185) However, a recently published cost-effectiveness study on the use of radiofrequency ablation (RFA) for BO by the same study group,(186) based on more recent cancer risk estimates in BO, found that initial RFA was not cost effective for patients with NDBO within the range of plausible rates of progression of BO to OAC, while it might be cost-effective for confirmed and stable LGD. For patients with HGD, initial RFA was more effective and less costly than endoscopic surveillance. In addition, there remain many unanswered questions regarding the durability of the ablation procedure and the need for endoscopic surveillance after ablation. Sharma *et al.* reported on three cases of sub-squamous neoplasia including two developing OAC after RFA, highlighting the need for continued meticulous surveillance with biopsies of neo-squamous epithelium, even after apparently successful eradication of intestinal metaplasia.(187) If endoscopic ablation in low-risk BO is applied in practice, it should therefore only be performed within a trial.

Potential role of chemoprevention—The relatively low absolute risk for OAC in all patients with BO means that the number needed to treat to prevent one cancer is high. Consequently, any intervention must be inexpensive and safe. Chemoprevention could be an adjunct to increase the length of surveillance intervals or even replace endoscopic surveillance in some BO patients. So far, proton pump inhibitors (PPIs), statins, and non-steroidal anti-inflammatory drugs (NSAIDs) have been the most extensively studied drugs for this purpose. It should be noted that most studies evaluated the treatment effects on surrogate markers for cancer development. In addition, due to non-randomised study designs, lack of association in some studies may have resulted from confounding by indication, in particular in the setting of PPIs.

The role of acid suppression with proton pump inhibitors (PPI) as a protecting factor for OAC development in patients with BO is controversial. Evidence exists that PPI therapy in BO reduces oesophageal acid exposure,(188) decreases mucosal cell proliferation and increases differentiation,(189) and possibly reduces the length of Barrett's segment as well as the incidence of dysplasia.(190–192) Others, however, did not find any effect of longstanding PPI treatment on the incidence of OAC in BO, and OAC has still been reported to occur after successful medical and surgical therapies for GORD.(193) In addition, the wide introduction of PPIs over the past 20 years did not prevent the rising incidence of BO and OAC in the general population. This may reflect inadequate acid suppression, as studies have shown that normalisation of acid exposure may not be achieved in 30–40% of BO patients, even when using doses of PPI up to four times the standard daily dose.(194, 195) At present, PPIs should be prescribed to control symptoms and oesophagitis, and there is as yet no evidence that high-dose maintenance treatment adequately prevents progression to neoplasia.

Based on observational studies and in vitro studies, other candidate chemoprevention agents are HMG CoA reductase inhibitors (aka "statins"). They have been shown to promote apoptosis in several *in vitro* models of human cancers.(196) In a recent study from Netherlands, 570 BO patients were prospectively followed for a median of 4.5 years. In this cohort, long-term use of statins (median duration of 5 years) was associated with a 54% reduction in the risk of malignant progression of BO. A combination of NSAIDs and statins was associated with a risk reduction of 78% ($P = 0.028$).(197) A nested case-control study in a U.S. cohort of BO patients also reported a significant inverse association between statin use and the risk of OAC in patients with BO in the setting of high prevalence of PPI use (OR 0.55; 95% CI 0.36–0.86).(198) There was a significant trend toward greater risk reduction with longer duration of statin use, however, the strong inverse associations with even short periods of use raise concerns of uncontrolled confounding.

The best evidence for any chemoprevention probably comes from NSAIDs, which may decrease cancer risk by reducing inflammation, mainly through the inhibition of COX-2 enzyme activity, which has tumour-promoting and anti-apoptotic properties.(199) By inhibition of prostaglandin production and inflammation induced by mitogens or growth factors, NSAID use might decrease cellular proliferation and oxidative damage from free-radical production. COX2 expression is increased in BO compared with healthy oesophageal epithelium.(200–202) In rats, COX2 inhibitors inhibit the development of adenocarcinoma

induced by reflux.(203, 204) Several human studies on the role of NSAID in lowering the risk of OAC have suggested a protective effect. Corley *et al.* demonstrated in a meta-analysis of 9 observational studies (2 cohort, 7 case control) significantly lower risks of oesophageal cancer among those who frequently use NSAIDs or aspirin compared with never users (OR 0.57; 95% CI 0.47–0.71).(205) Any use of aspirin or other NSAID was inversely associated with both oesophageal adenocarcinoma and squamous cell carcinoma. Another meta-analysis reported relative risks of oesophageal cancer of 0.51 (0.38–0.69) for aspirin use and 0.65 (0.46–0.92) for NSAID use.(206) In a prospective cohort study with 350 BO patients, those who took aspirin or other NSAID regularly had a substantially lower incidence of oesophageal adenocarcinoma, aneuploidy, and to a lesser extent, tetraploidy, compared with those who did not take such drugs regularly.(207) In the Dutch study mentioned above, use of NSAIDs was associated with 53% lower risk of progression to HGD/OAC ($P = 0.03$). (197) Whether the chemopreventive benefits of NSAIDs outweigh the potential cardiovascular side effects, risk of GI bleeding and nephrotoxicity associated with chronic use, remains controversial. The prescription of low-dose aspirin could be considered for patients with BO who also have risk factors for cardiovascular disease, and the concomitant use of a PPI should decrease the risk of serious GI complications.(10) Large randomized controlled trials on the chemopreventive effect of NSAIDs are needed, which in particular are not affected by confounding by indication. The Aspirin Esomeprazole Chemoprevention Trial (Aspect), will provide a more definitive assessment of the effects of acid suppressing medications and aspirin as chemoprevention agents in BO. The results from this trial are anticipated in the near future.(208)

Summary and future directions

Barrett’s oesophagus is a common disorder in western countries, and appears to have a persistent increasing incidence in the general population, with obesity being the susected most important driving factor for the increasing incidence. The increasing incidence heralds a further increase in OAC incidence in the coming decades, and emphasizes the need for effective preventive strategies. At present, however, screening cannot be recommended as the population at risk is too broadly defined, and current screening techniques are burdensome and costly. More research is anticipated on the development of less invasive and more cost-effective modalities for detection of BO, as well as on the development of non-endoscopic markers that can predict presence of BO.

With recent studies showing much lower cancer risk in BO than previously anticipated, and the growing emphasis on health care cost containment, the rationale for endoscopic surveillance is likely to come under greater scrutiny. The risk of OAC among patients with BO is so minor that in the absence of dysplasia, routine surveillance of such patients is of dubious value. BO patients with short segments of BO without dysplasia are the least likely to benefit, and surveillance could be omitted, especially when other clinical risk factors are absent. In LSBO patients in whom absence of dysplasia can be confirmed repeatedly, it may be reasonable to extend further surveillance intervals from the currently proposed 3 years to 5 years or even longer. Moreover, the increasing use of endoscopic ablation therapy in NDBO patients is at present not justifiable outside clinical studies. Future studies should focus on the development of a risk score that incorporates demographic, endoscopic and

histologic risk factors, and on improvement of optical recognition of dysplasia. Prospective multicenter study with inclusion of a significant number of uncomplicated BO patients and randomisation to clinical factors and biomarkers are needed. Furthermore, large prospective randomised clinical trials on chemopreventive agents are eagerly awaited.

Abbreviations

BMI	Body mass index
BO	Barrett's oesophagus
GORD	Gastro-oesophageal reflux disease
HGD	High-grade dysplasia
LGD	Low-grade dysplasia
LSBO	Long segment Barrett's oesophagus
NBI	Narrow band imaging
ND	No dysplasia
NDBO	Non-dysplastic Barrett's oesophagus
OAC	Oesophageal adenocarcinoma
OGD	Oesophago-gastro-duodenoscopy
RFA	Radiofrequency ablation
SSBO	Short segment Barrett's oesophagus
UK	United Kingdom
US	United States
VAT	Visceral adipose tissue

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Dilemmas with screening for Barrett's oesophagus.

- Significant proportion of BO patients and those with OAC lack reflux symptoms.
- At risk population for BO is too broadly characterized.
- Endoscopy is invasive and expensive as a screening tool

Dilemmas with surveillance of Barrett's oesophagus.

- Overall risk of OAC in BO is low.
- Only few patients will eventually die from oesophageal cancer
- Most cancers are detected outside surveillance programs
- Biopsy sampling error due to patchy distribution of dysplasia
- Suboptimal adherence to rigorous biopsy protocol in daily practice
- Interobserver variability in diagnosing the presence and degree of dysplasia, even among expert GI pathologists
- Natural history of dysplasia is unclear
- Surveillance is burdensome for patients
- Current practice is not cost-effective

Table 1.

Overview of results from meta-analyses on oesophageal adenocarcinoma (OAC) risk in patients with Barrett's oesophagus (BO).

Reference	Studies (*n*)	OAC Incidence rate* (95% CI)	HGD/OAC Incidence rate (95% CI)
Shaheen et al. (2000)	25	5.0 (x-x)	--
Chang et al. (2007)	14	6.3 (3.6–10.1)	--
Thomas et al. (2007)	41	7 (6–9)	9 (5–16)
Yousef et al. (2008)	47	4.1 (3.1–5.5)	9.3 (6.3–14)
Wani et al. (2009) *NDBO* *LGD*	45 16	6,0 (5.1–6.9) 17 (13–21)	-- --
Sikkema et al. (2010)	50	6.3 (4.7–8.4)	10.2 (7.5–14)
Desai et al. (2012) *NDBO*	57	3.3 (2.8–3.8)	--

*Incidence rate per 1000 person years

**NDBO: non dysplastic Barrett's oesophagus; LGD: low-grade dysplasia; HGD: high grade dysplasia; OAC: oesophageal adenocarcinoma; CI: confidence interval

Table 2.

Overview of results from nation-wide population-based incidence studies of oesophageal adenocarcinoma (OAC) in unselected patients with Barrett's oesophagus (BO).

Variable	BO patients (*n*)	Incident OAC (*n*)	Person-years of follow up	OAC incidence (% per year)	95% confidence interval
de Jonge et al. (2010)	42.207	337	234.821	0.14	0.12–0.16
BO all	25.890	259	136.316	0.19	0.17–0.21
Male	16.317	78	97.505	0.08	0.07–0.10
Female					
Bhat et al. (2011)	8.522	79	59.784	0.13	0.10–0.16
BO all	4.936	19	34.493	0.17	0.13–0.22
Male	3.586	60	25.272	0.08	0.05–0.12
Female					
Hvid-Jensen et al. (2011)	11.028	66	56.782	0.12	0.09–0.15
BO all	7.366	56	37.771	0.15	0.11–0.19
Male	3.662	10	19.011	0.05	0.03–0.10
Female					

Table 3.

Guidelines for endoscopic surveillance of Barrett's oesophagus (BO) by major gastroenterological societies.

Grade of dysplasia	ACG	ASGE	AGA	BSG	SFED
NDBO	2 OGD within first year, then every 3 years if still NDBO	2 OGD within first year, then every 3 years if still NDBO	2 OGD within first year, then every 3–5 years if still NDBO	OGD every 2 years if still NDBO	SSBO (< 3 cm): OGD every 5 yearsLSBO (3 – 6 cm): OGD every 3 yearsLSBO (> 6 cm): OGD every 2 years
LGD	Repeat OGD within 6 months; if no HGD, then every 1 year	Repeat OGD within 6 months; if no HGD, then every 1 year	Repeat OGD within 6 months; if no HGD, then every 6–12 months	Repeat OGD within 3 months; if no HGD, then every 6 months	Repeat OGD. If low grade confirmed, OGD at 6 months, 1 year, then yearly
HGD	Repeat OGD within 3 months to rule out OAC, then every 3 months or endoscopic/surgical therapy	Repeat OGD within 3 months to rule out OAC, then every 3 months or endoscopic/surgical therapy	Repeat OGD within 3 months to rule out OAC, then every 3 months or endoscopic/surgical therapy	Repeat OGD within 3 months to rule out OAC, then every 3 months or endoscopic/surgical therapy	Repeat OGD.If high grade confirmed, endoscopic or surgical treatment

NDBO: non dysplastic Barrett's oesophagus; LGD: low-grade dysplasia; HGD: high grade dysplasia; OGD: oesophagogastroduodenoscopy; SSBO: short segment BO; LSBO: long segment BO