REVIEW

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Natural History of Barrett's Esophagus

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Abstract

Barrett's esophagus (BE) is a very common condition. We have obtained fairly profound knowledge of the natural history of this condition. This results from many cross-sectional and cohort studies, many describing patients undergoing long-term surveillance. Their consent to use their clinical data has improved our knowledge to the benefit of these same and other patients. The prevalence of BE increases with age both in men and in women. This increase starts at a younger age in men than in women. The incidence of high-grade dysplasia and cancer in BE depends on segment length, gender, and age. The latter two likely indicate the duration of the presence of BE in an individual patient. Other factors that influence the incidence of dysplasia and cancer are smoking behavior and use of certain medications such as PPIs, statins, and NSAIDs. Surveillance of BE and treatment of dysplasia can impact the incidence of and mortality due to esophageal adenocarcinoma. This is of major benefit to a subgroup of BE patients. The epidemiology and burden of disease ask for further efforts to develop targeted screening, surveillance, and intervention techniques in coming years.

Keywords Barrett's esophagus · Esophageal adenocarcinoma · Surveillance · Progression · Epidemiology · Prevention

Introduction

Almost one quarter of all human cancers arise in the gastrointestinal tract, the predominant cancer-affected tract in the human body. Remarkably, nearly all these malignancies are for long preceded by precursor lesions that can be visualized in detail with modern techniques. This provides major opportunities for screening, surveillance, and targeted intervention. As a result, most physicians managing patients with gastrointestinal disorders are used to deal with premalignant lesions, although the actual risks associated with different conditions are not always fully understood. The high cancer incidence in the gastrointestinal tract relates to a variety of factors. These include surface area, tissue turnover, and frequent exposure to internal and external factors that may induce tissue damage and chronic inflammation. This is all best illustrated at the gastroesophageal junction, arguably the segment of the gastrointestinal tract with the highest cancer incidence per segment length. Of note, this remarkably high cancer incidence
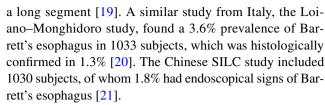
is of recent date and seems to occur in many populations worldwide although at different moments in time. These differences relate to changes in lifestyle and risk factors for Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC).

Epidemiology of Barrett's Esophagus

Exposure to gastroduodenal refluxate including acid and bile often leads to gastroesophageal reflux disease (GERD). This condition is among others characterized by chronic inflammation of the lining of the lower esophagus. GERD is very common in Western populations and increasing elsewhere such as in the far east [2, 11]. It is the most common GI-related diagnosis in the USA [1]. A systematic review of 28 studies from different countries reported that the prevalence of GERD in adult populations ranged between 18 and 28% in North America, 9–26% in Europe, 9–33% in the Middle East, and 2.5–8% in East Asia [2]. This prevalence had increased with an approximate 50% in 20 years. The same study also included two studies reporting a GERD incidence of 4.5–5.4 per 1000 person-years in the UK and USA [2]. This explains that acid-suppressive drugs, in particular proton pump inhibitors, are since long among the most commonly used drugs in the Western world.

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This increase in GERD is accompanied by a rapid increase in prevalence of Barrett's esophagus, the main target for prevention of esophageal adenocarcinoma. The exact prevalence of BE in different populations is difficult to assess because the condition by itself is asymptomatic, and a diagnosis is made only when an endoscopy is performed. The latter is usually done for persistent GERD symptoms, which creates a selection bias. However, there are various data that provide solid ground for the assumption that Barrett's metaplasia is a common condition in adults in populations with a high prevalence of GERD. Almost 30 years ago, a first autopsy study reported seven (0.95%) BE cases in 733 unselected autopsies in the USA [12]. Only five cases were diagnosed at autopsy, a first indication that the majority of BE cases remain undiagnosed during their lifetime. Further information on the prevalence of BE came from endoscopy studies. In a large Dutch primary care database covering more than 500,000 subjects, we noted that patients were newly diagnosed with Barrett's esophagus at a rate of 40.5 per 1000 upper gastrointestinal endoscopies in 2002 [13]. This rate had markedly increased over time. A recent renewed analysis of the same, now expanded database in combination with similar data from the UK, showed that the rate of newly diagnosed BE cases had stabilized since the previous publication [14]. Similar changes over time are now occurring in Asia. A recent analysis of 51 endoscopy studies, mainly from Eastern Asia, including 453,147 patients noted a pooled prevalence of endoscopic Barrett's esophagus of 7.8% (95% CI 5.0–12.1) and of histologically confirmed Barrett's metaplasia of 1.3% (0.7–2.2) [15]. These data are in line with other series. It should be noted that these were procedures for clinical indications, and thus included the major confounder of procedures being performed for GERD symptoms. In order to overcome this confounder, some studied the prevalence of BE in subjects undergoing screening colonoscopy. In such a study from the USA, a 6.8% prevalence was found in 961 subjects [16]. In another US study investigating 300 subjects above the age of 64 years referred for screening colonoscopy, a 16.7% prevalence of BE was observed [17]. In a similar Dutch study, we observed an approximate 7% prevalence of Barrett's esophagus among 382 colonoscopy screenees with an average age of 53 years (results unpublished).

Several population-based studies have provided further insights. Among 11 studies reporting the prevalence of upper GI pathology in general populations, three reported on the prevalence of Barrett's esophagus [18]. The first was the Swedish Kalixanda study. Among 1000 Swedish adults undergoing upper gastrointestinal endoscopy as part of a population prevalence study, an endoscopic BE segment was observed in 10.3% of the subjects. In 9.9%, histology confirmed the presence of columnar epithelium, while specialized intestinal metaplasia was observed in 1.6% of them. Of those subjects, 1.1% had a short BE segment and 0.5%

a long segment [19]. A similar study from Italy, the Loiano–Monghidoro study, found a 3.6% prevalence of Barrett's esophagus in 1033 subjects, which was histologically confirmed in 1.3% [20]. The Chinese SILC study included 1030 subjects, of whom 1.8% had endoscopical signs of Barrett's esophagus [21].

More detail on the prevalence of Barrett's esophagus in different populations is provided by studies on age- and sex-related distribution of Barrett's esophagus prevalence. A study from the UK on 21,899 first endoscopies observed that the prevalence of BE rose with 7.4% for each additional year of age between the age of 20 and 59 year in males. It showed a similar pattern albeit with a 20-year delay in females [4]. This pattern was confirmed in a Dutch primary care population as well as in Northern Ireland [22, 23].

Predisposing Factors to Barrett's Esophagus

Gastroesophageal reflux is considered the predominant risk factor for Barrett's esophagus. The risk seems to correlate with the severity and duration of GERD. A study from the USA based on cross-sectional data from 683 Veterans Affairs patients reported that onset of GERD before the age of 30 years and the presence of weekly symptoms were together associated with a 15-fold increased risk of Barrett's esophagus [3]. Other factors include male gender, white race, cigarette smoking, and central adiposity [4, 5]. Many studies have also reported an inverse correlation between colonization with *Helicobacter pylori* and presence of Barrett's esophagus [3]. These factors interplay with genetic predisposition. Barrett's esophagus shows a certain degree of familial clustering. In a Dutch survey of 603 patients, definite familial clustering was found in 7% of patients [6]. This was likely an underestimate of the true prevalence of familial clustering, since a further 44% of participants reported that familial co-occurrence was either unknown or likely. Recent large population case–control studies identified more than 20 genetic variants predisposing for Barrett's esophagus in populations of European ancestry [7, 8].

Risk Prediction

Together, this knowledge led to a range of tools to predict the presence of Barrett's esophagus in specific populations. Most of these were based on demographic and clinical data alone. These models tend to have fair performance in predicting the likelihood that a subject will have Barrett's esophagus. A recent study aimed to combine these with familial history [9]. Based on close to 900 Barrett's cases, the authors developed a model using eight risk factors including age, sex, smoking, heartburn frequency, and use of acid suppressants. They combined this with family history. For 50-year-old subjects, the model predicted Barrett's

esophagus prevalences ranging between 3 and 33% in men, and 0.5 and 10% in women [9]. A recent study went further and aimed to predict the risk of Barrett's esophagus and esophageal adenocarcinoma based on demographic and lifestyle data in combination with an individual's genetic profile [10]. The authors analyzed 3288 Barrett's cases, 2511 patients with esophageal adenocarcinoma, and 2177 controls from different cohorts. Subjects were assessed for GERD symptoms as well as age, sex, smoking habits, body mass index, and use of NSAIDs. Similar to previous models, these factors were moderately accurate to discriminate between Barrett's cases and controls with an area under the curve ranging between approximately 0.64 and 0.67 for demographics plus lifestyle factors alone and GERD history alone, and 0.79 when combining both. Each individual was further assigned a polygenic risk score based on their number of risk alleles (0, 1, or 2) for each of 23 genetic variants identified as being associated with Barrett's esophagus. For each variant, the allele number was weighted in relation to the effect estimate of the genetic variant. The sum of these weighted allele counts was then divided by 23 to yield one polygenic risk score [10]. Adding the polygenic risk score to the other factors only marginally increased prediction accuracy with an AUC of 0.799 for all factors combined. The authors rightfully concluded that the small contribution of genetic data to their prediction tool does not justify their clinical use.

Progression of Barrett's Esophagus

These data are all relevant for an adequate understanding of the natural history of Barrett's esophagus. They provide insight into the occurrence of Barrett's metaplasia in men and women, and a background to determine progression rates to dysplasia and cancer. These two then appear closely linked, as we will discuss. Similar to the development of knowledge on the epidemiology of Barrett's esophagus, the first knowledge on progression rates to dysplasia and cancer also came from endoscopy series, in particular from tertiary care centers. One of the oldest cohorts in this respect was the Rotterdam cohort. It consisted of a cohort of 166 patients diagnosed between 1973 and 1986, and followed since then. They first did not receive endoscopic surveillance; this started in 2001. The most recent analysis of this cohort included 130 patients with an average age at initial diagnosis of 62.4 years (range 14.4–92.3 years) and an average follow-up of 14.7 years (range 2.1–32.0) [24]. Thirteen patients developed high-grade dysplasia (HGD) or esophageal adenocarcinoma (EAC) during follow-up, corresponding with a rate of 1 per 151 patient-years or 0.66% per year (95% CI 0.58–74). Many other studies came with similar data, although often with limited patient numbers and short

duration of follow-up. Together, these expanding series were over time repeatedly subjected to systematic reviews and meta-analyses. These meta-analyses consistently reported progression rates to cancer varying between 2.2 and 6.3 per 1000 patient-years when focusing on all Barrett's patients [25–29]. Further reviews taught that the risk was in the low range for patients with non-dysplastic Barrett's at a rate of 3.3 (2.8–3.8) and only 1.9 per 1000 years for patients with short-segment BE [30]. A recent US and Dutch multicenter study reported no progression to high-grade dysplasia or cancer in 167 short-segment (< 1 cm) non-dysplastic BE cases [31]. In contrast to these findings in patients with short and non-dysplastic BE, the rate of cancer tended to be higher in patients with BE and low-grade dysplasia. A systematic review of 24 studies with 2694 patients followed for at least 2 years reported an annual progression rate to cancer of 5.4 (3.2–7.6) per 1000 years, and progression to high-grade dysplasia or cancer combined of 17.3 (9.9–24.7) per 1000 patient-years [32] (Table 1). Most of these studies relied on single pathologist's evaluation per patient. Since the diagnosis of dysplasia is investigator dependent, more stringent criteria ask for confirmation of dysplasia by a second pathologist. This often leads to down-staging of a proportion of patients. This in turn may affect disease progression rates. This was illustrated by a recent study that re-assessed low-grade dysplastic samples of 231 BE patients [33]. Low-grade dysplasia was confirmed in 161 (70%); the remainder was mostly downgraded to no dysplasia or indefinite for dysplasia. Two patients were upgraded to high-grade dysplasia. In patients with confirmed low-grade dysplasia, the subsequent incidence of high-grade dysplasia and EAC combined was 5.18 (3.63–7.19), and the incidence of EAC alone 2.51 (1.49–3.99) per 100 patient-years [33]. One study of 68 BE patients with low-grade dysplasia even reported progression to EAC alone, respectively, in combination with HGD in approximately 3 and 8.5% of patients per year [34].

The highest progression rates to cancer are not surprisingly noted in patients with high-grade dysplasia. Determination of their progression rates is confounded by the fact that HGD patients form only a small minority of BE patients that nowadays routinely undergoes intervention such as endoscopic resection. This precludes determination

Table 1 Incidence per 1000 patient-years of neoplastic progression among BE patients with no dysplasia (ND) and low-grade dysplasia (LGD)

	HGD and EAC	EAC
ND	5.2 (95% CI 4.1; 6.6) [50]	3.3 (95% CI 2.8; 3.8) [30]
LGD	17.3 (95% CI 9.9; 24.7) [32]	5.4 (95% CI 3.2; 7.6) [32]
ND and LGD	5.8 (95% CI 4.7; 7.2) [50]	4.3 (95% CI 3.4; 5.5) [50]

HGD high-grade dysplasia, *EAC* esophageal adenocarcinoma

of natural progression rates to esophageal adenocarcinoma. Nevertheless, one systematic review included four original studies of 236 BE patients with HGD that were followed for at least 6 months without intervention. The progression rate to cancer in these patients with high-grade dysplasia was 6.58 (4.97–8.19) per 100 years [35]. This frequent diagnosis of invasive cancer in patients with high-grade dysplasia firstly reflects the co-existence of these lesions and the subtleties of histopathological diagnosis, and secondly likely also is a measure of true progression. This forms the basis for guideline recommendations to assess dysplastic samples with two pathologists, and manage high-grade dysplasia and cancer by means of expert high-resolution endoscopy and endoscopic resection if possible. This first enables further staging and may also form adequate treatment depending on histology [36–38].

Factors that Influence the Natural History of Barrett's Esophagus
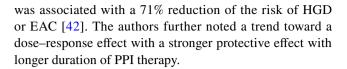
Barrett's Segment Length

As mentioned, the risk of progression to HGD or EAC seems very low in patients with short-segment BE. Conversely, the risk may increase in relation to BE segment length. This was confirmed in a recent US study on 1175 BE patients followed for an average 5.5 years [39]. The risk of HGD and EAC combined was 0.31% per year for those with a BE segment < 3 cm and increased 1.28-fold with every extra cm to 2.41% for those with a BE segment > 13 cm. These findings were supported by others [40].

Proton Pump Inhibitors

In a prospective cohort of 540 BE patients followed for 5.2 years, treatment with a proton pump inhibitor during follow-up was associated with an hazard ratio of 0.21 (0.07–0.66) for progression to HGD or EAC [41]. A meta-analysis of this and six other studies concluded that PPI use

was associated with a 71% reduction of the risk of HGD or EAC [42]. The authors further noted a trend toward a dose–response effect with a stronger protective effect with longer duration of PPI therapy.

NSAIDs and Statins

Several studies reported that both NSAIDs and statins alone and in combination also decreased the risk for progression of BE [43–45]. The individual studies reported relative risks for NSAID and statin use alone ranging for each between 0.45 and 0.65, with one study reporting that the combination further augmented the effect leading to a hazard ratio of 0.22 [44].

Tobacco Smoking

One study from Ireland reported that smoking was associated with a hazard ratio of 2.03 (1.29–3.17) for progression to HGD or EAC [46]. Other studies reported non-significant associations between smoking and BE progression.

A recent systematic review and meta-analysis combined these studies and confirmed that the risk of progression to HGD or EAC in BE patient was firstly determined by the presence or absence of low-grade dysplasia with an odds ratio of 4.2 (2.1–8.5) [47] (Table 2). The risk of progression to HGD or cancer further significantly increased with increasing BE segment length with an odds ratio of 1.2 (1.1–1.3) per additional cm in length. The study further confirmed that use of a PPI or statin significantly decreased the risk of progression to HGD or cancer, while the protective effect of NSAID use was of borderline significance [47]. Finally, the systematic review confirmed that higher age and male sex are risk factors for disease progression. Although reported as separate factors, various studies have suggested that these are actually interrelated and together a reflection of the duration of presence of BE. Males on average have a lower age of onset of BE, and thus at any given age a higher likelihood of long disease duration. A Dutch cohort study suggested that HGD and cancer in particular occurred after

Table 2 Patient characteristics and risk of neoplastic progression to HGD/EAC in Barrett's esophagus

Patient characteristic		Risk estimation
Age [47]		OR 1.03 (95% CI 1.01; 1.05)
Male gender [47]		OR 2.16 (95% CI 1.84; 2.53)
Length of BE segment (per additional cm) [47]		OR 1.25 (95% CI 1.16; 1.36)
Proton pump inhibitors [47]		OR 0.55 (95% CI 0.32; 0.96)
NSAIDs and statins	NSAIDs [44]	HR 0.47 (95% CI 0.24; 0.93)
	Statins [47]	OR 0.48 (95% CI 0.31; 0.73)
	Combination [44]	HR 0.22 (95% CI 0.06; 0.85)
Tobacco smoking [46]		HR 2.03 (95% CI 1.29; 3.17)
Low-grade dysplasia [47]		OR 4.25 (95% CI 2.58; 7.0)

an "incubation period" of at least 30 years [24]. A British study suggested a 17-year delay in development of BE in women compared to men [48]. Together, these phenomena can explain male gender and age as risk factors for progression to HGD and cancer [47].

Population Picture

Together, these data allow constructing population overviews. This provides a picture with GERD as most common clinical diagnosis in Western countries. A distinct proportion of them develops Barrett's esophagus. We do not see Barrett's metaplasia gradually develop over time in GERD patients undergoing repeat endoscopy, but we do know that the prevalence of BE steadily increases with age with a time gap between men and women. Data on the prevalence of BE in symptomatic patients undergoing diagnostic endoscopy are by definition biased. However, studies into the prevalence of BE in other populations such as subjects undergoing screening colonoscopy, and true population studies evaluating the prevalence of BE in unselected subjects provide more reliable information [16–21]. These studies reported a rather steady 3–10% prevalence of BE, with some variation above and below these borders. The differences without doubt in part relate to the population and age-group studied, as well as to the definition of BE. Some studies for instance reported on the prevalence of endoscopic signs of BE metaplasia and the histopathological prevalence of, respectively, columnar metaplasia and specialized intestinal metaplasia. If we would accept the 7% prevalence of BE among Dutch 50+ year olds as previously observed in colonoscopy screenees, this would translate to approximately 308,000 BE carriers among 4.4 million subjects. With an approximate 1500 esophageal adenocarcinomas per year in the same population, the annual incidence of EAC among all BE carriers would approximate 0.49%.

Another approach can be based on all identified BE cases in the Netherlands, in combination with the fact that we know that no more than 5–10% of EAC patients had been known with BE prior to their cancer diagnosis [49]. In the Netherlands in 2010, close to 42,500 subjects had been identified by histology with BE [50]. If these indeed represented a maximal 10% of all BE cases, their total would amount to at least 425,000. Assuming that these cases in particular affect subjects aged 50 years and above, it would

be equivalent with a 9% prevalence of BE in this subgroup of the total population. The annual 1500 cases would then be equivalent to an annual incidence of EAC among all BE carriers of approximately 0.35%.

One quickly realizes that both combinations are rough estimates. The beauty is that they allow providing an overall population picture that then can be used for public health discussions. The picture also makes clear that a 1% population prevalence of BE as sometimes suggested does not match cancer incidence data. Again, for the Dutch situation this would match 44,000 BE cases among 4.4 million 50+ year olds. This would imply that nearly all BE cases have been identified in this country, and that the cancer incidence among these BE cases would approximate 3% per year, or six- to tenfold the rate of any cohort study with the exception of studies on HGD. Both implications are unlikely and not supported by the literature. These epidemiological exercises also illustrate the correlation between population prevalence of BE, cancer incidences among BE cases, and resulting EAC cases per year, with the latter number being the most solid and based on cancer registries. The given number of cancer cases thus translates back in the interrelated BE prevalence and cancer incidence.

These data were in recent years supported by three large population studies (Table 3). The first and largest came from the Netherlands and reported on 42,207 BE patients identified in the Dutch national histopathology registry [50]. Among patients undergoing endoscopic surveillance, the annual incidence of EAC was 0.4%. However, the cancer incidence was 0.14% overall for the total cohort when also including all BE patients who did not undergo surveillance. Two similar studies with, respectively, 11,000 Irish and 8500 Danish patients had very similar results with cancer incidences of 0.13 and 0.15% [51, 52]. These consistent data from three population studies in Western Europe with large patient numbers suggest that the overall incidence of EAC in unselected BE cases is low. As mentioned, this matches with a high prevalence of BE in the general population.

Natural History of BE and Benefits of Screening and Surveillance

These data are very relevant to determine optimal cancer prevention strategies. Modeling studies for instance showed that the cost efficacy of BE surveillance strongly depended

Table 3 Population-based incidence studies of esophageal adenocarcinoma (EAC) in unselected patients with Barrett's esophagus

Country	BE patients (n)	Incident EAC (n)	Person-years follow-up	EAC incidence (% per year)	95% confidence interval
The Netherlands [50]	42,207	337	234,821	0.14	0.12–0.16
Ireland [51]	8522	79	59,784	0.13	0.10–0.16
Denmark [52]	11,028	66	56,782	0.12	0.09–0.15

on cancer incidence [53–56]. These modeling studies generally tend to use higher cancer incidences than reported in the above-mentioned population studies. Papers on BE, whether original studies, reviews, or guidelines, often start with statements such as that EAC is the most rapidly increasing cancer in the world [34] and the fastest growing cause of cancer mortality [36]. Statements such as these find a source in the fact that EAC has shown a proportional dramatic increase in Western populations over the past 40 years. However, despite this proportional increase, both statements are untrue and likely to remain untrue for long. When looking at GI-tract cancers alone, mortality worldwide due to gastric, colorectal, liver, and pancreatic cancer remains far more common than mortality due to esophageal adenocarcinoma. Further, mortality due to colorectal, liver, and pancreatic cancer rose more in absolute numbers in the period of 1990–2013 than mortality due to esophageal cancer [57]. This is true on a global basis, but in Western countries alone. Even in regions such as North America and Western Europe with the highest EAC incidence, it remains a rare malignancy roughly making up for 1% of all cancers [58]. Unfortunately, 5-year survival rates remain poor with only 20% [58]. This survival only slowly increased over the past 40 years.

All together, we are thus faced with a major clinical and public health problem. At a time of decreasing prevalence of *Helicobacter pylori* and increasing prevalence of obesity, we are faced with GERD affecting a substantial part of the adult population worldwide. A considerable proportion of GERD-affected subjects develop BE. This means that many countries will have to take into account that many of their 50+ year olds carry BE, even when undiagnosed in most of them. A small proportion of these subjects annually progress to HGD and EAC. At an early stage, these conditions can be treated by ablative techniques with limited burden and risks. However, at an advanced stage, EAC requires invasive treatment with considerable burden, costs, and mortality. In recent years, treatment for invasive EAC has shown marked improvements with introduction of presurgical chemoradiotherapy [59]. Further efforts are ongoing to see whether chemoradiotherapy can provide curative options and thus replace surgery in certain EAC patients [60]. Nevertheless, prevention and early detection remain by far the most attractive strategy to manage EAC. Together, the high prevalence of BE and the low cancer incidence among unselected BE cases, versus the burden of treatment and low survival of EAC ask for smart strategies to select BE patients who are most likely to benefit from surveillance and intervention. These do not include short-segment BE cases, nor the majority of those without dysplasia [61]. A recent multicenter study based on 2697 BE patients developed a scoring system based on gender, smoking status, BE length, and the presence of low-grade dysplasia to classify patients at low, intermediate, and high risk [62]. During a 7-year follow-up,

progression to HGD and EAC occurred in 0.5, 4.6, and 12.3%, respectively.

Conclusions

With many patients undergoing long-term surveillance and providing consent to use their data to improve our knowledge and benefit others, and many researchers worldwide reporting their analyses of these data, we have obtained a major understanding of the natural history of BE. BE is a common condition, with a prevalence increasing with age in men and women, although with a delay in women. The incidence of HGD and cancer in BE depends on segment length, gender, and age, both likely a marker for the length of presence of BE, the presence or absence of low-grade dysplasia, and other factors such as smoking behavior and use of certain medications such as PPIs, statins, and NSAIDs. Targeted use of surveillance and intervention can impact the incidence and mortality due to EAC and is of major benefit to a subgroup of BE patients. The epidemiology and burden of disease ask for further efforts to develop targeted screening, surveillance, and intervention techniques in coming years.

Key Messages

- The prevalence of GERD has increased with approximately 50% in the last 20 years.
- The presence of BE has increased simultaneously, in Western countries leading to an estimated population prevalence reaching 3–10%.
- GERD, male gender, white race, cigarette smoking, and central adiposity are the most common risk factors for Barrett's esophagus.
- Women develop BE at a later age than men.
- Neoplastic progression in BE depends on age, gender, segment length, use of proton pump inhibitors, NSAIDs and statins, tobacco smoking, and the presence of dysplasia.

Compliance with ethical standards

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