

Barrett's oesophagus and oesophageal adenocarcinoma: time for a new synthesis

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Abstract | The public health importance of Barrett's oesophagus lies in its association with oesophageal adenocarcinoma. The incidence of oesophageal adenocarcinoma has risen at an alarming rate over the past four decades in many regions of the Western world, and there are indications that the incidence of this disease is on the rise in Asian populations in which it has been rare. Much has been learned of host and environmental risk factors that affect the incidence of oesophageal adenocarcinoma, and data indicate that patients with Barrett's oesophagus rarely develop oesophageal adenocarcinoma. Given that 95% of oesophageal adenocarcinomas arise in individuals without a prior diagnosis of Barrett's oesophagus, what strategies can be used to reduce late diagnosis of oesophageal adenocarcinoma?

Oesophageal specialized intestinal metaplasia

Specialized intestinal metaplasia is a differentiated epithelium with crypt architecture that resembles the epithelium of the intestine, rather than that of the oesophagus.

This paper concerns a condition whose existence is denied by some, misunderstood by others, and ignored by the majority of surgeons. It has been called a variety of names which have confused the story because they have suggested incorrect etiological explanations...

Norman Barrett, 1957

Barrett's oesophagus has been defined as a condition in which the normal stratified squamous epithelium of the oesophagus is replaced by metaplastic columnar epithelium, although no universally accepted definition currently exists^{1,2}. The columnar-lined oesophagus was described by Norman Barrett in 1950 (REF. 3), reported to be associated with gastroesophageal reflux disease in 1953 (REF. 4) and convincingly linked with oesophageal adenocarcinoma in 1975 (REF. 5). Unless detected early, oesophageal adenocarcinoma is a lethal cancer with a mortality rate greater than 85%, and for the past four decades its incidence has been increasing at an alarming rate in many regions of the Western world⁶. The paradigm is that Barrett's oesophagus arises as a complication of symptomatic gastroesophageal reflux disease and predisposes to oesophageal adenocarcinoma.

Treatment of Barrett's oesophagus has been based on this paradigm. Clinical guidelines initially endorsed endoscopic screening of individuals with symptomatic gastroesophageal reflux disease for Barrett's oesophagus and endoscopic biopsy surveillance of Barrett's oesophagus^{7,8}. Increased endoscopic detection and surveillance

of Barrett's oesophagus have provided valuable insights into the natural history of this condition, and research has identified challenges to reducing the incidence and mortality of oesophageal adenocarcinoma when clinical decisions are made on the basis of this paradigm. In this Review, we examine new data on the epidemiology of Barrett's oesophagus and oesophageal adenocarcinoma, the global distribution of these conditions, the biology of oesophageal specialized intestinal metaplasia, and somatic genomic alterations and evolutionary dynamics that predispose to oesophageal adenocarcinoma. A synthesis of these population, clinical, computational and laboratory advances can guide future research for the prevention and early detection of oesophageal adenocarcinoma.

Barrett's specialized intestinal metaplasia

The columnar epithelium of Barrett's oesophagus has a crypt architecture similar to that of the intestine, and it has been described as a specialized intestinal metaplasia^{1,2} (FIG. 1). It has recently been proposed that Barrett's specialized intestinal metaplasia is a successful adaptation to the harsh intra-oesophageal environment of chronic gastroesophageal reflux disease because it has acquired several functions not present in the normal oesophageal squamous epithelium⁹. Various studies are consistent with this hypothesis and indicate that the intestinal metaplasia is a well differentiated epithelium with several acquired functions that participate in mucosal defence¹⁰⁻¹⁵ (FIG. 1).

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At a glance

- The paradigm that Barrett's oesophagus develops as a consequence of symptomatic gastroesophageal reflux disease and predisposes to oesophageal adenocarcinoma has dominated clinical thought for more than three decades. However, current approaches for controlling the incidence and mortality of oesophageal adenocarcinoma, which are largely based on endoscopic investigation of individuals with symptomatic gastroesophageal reflux disease, and histology-guided surveillance and treatment of individuals with Barrett's oesophagus, have considerable limitations.
- Barrett's oesophagus rarely progresses to oesophageal adenocarcinoma, and a theory has recently been proposed that mucosal defences in most patients with Barrett's oesophagus represent successful adaptations to the harsh intra-oesophageal environment of chronic gastroesophageal reflux disease. Several mucosal defences that arise in Barrett's oesophagus have been identified, including the secretion of bicarbonate and mucous, expression of claudin 18 tight junctions, overexpression of defence and repair genes, and resistance to prolonged and repeated acid exposure.
- The incidence of oesophageal adenocarcinoma has been rising at an alarming rate in the United States, Western Europe, Australia and in other developed countries over the past four decades, and there is disquieting evidence of increased incidence of oesophageal adenocarcinoma in some Asian populations.
- Four risk factors — gastroesophageal reflux disease, obesity, cigarette smoking and poor diet — account for most oesophageal adenocarcinomas. The effects of obesity might influence both early and late stages of progression and interact biologically with gastroesophageal reflux disease, although a substantial proportion of the effect of obesity is likely to be through other pathways.
- Neoplastic progression to oesophageal adenocarcinoma is characterized by genomic instability (including chromosomal instability in most cases), disruption of regulatory pathways and temporal evolution of clones that might be modulated by host and environmental risk and protective factors. Proper measurement and quantification of the complexity of these alterations creates opportunities and challenges for improved risk stratification, prevention and early detection.
- Aspirin and other non-steroidal anti-inflammatory drugs have been consistently reported to have a protective association with oesophageal adenocarcinoma in case-control and cohort studies as well as meta-analyses; they might be useful in patients at both early and late stages of progression.
- No intervention, whether based on lifestyle modification, chemoprevention or medical and surgical treatments, has yet been convincingly demonstrated in a randomized trial to reduce the incidence and/or mortality of oesophageal adenocarcinoma; this remains a particularly crucial area of unmet research need. New oesophageal adenocarcinoma prevention strategies are proposed to overcome these limitations.

Person-years

The denominator used in calculation of an incidence rate. It takes into account both the number of people being observed and the period of observation. For example, 1,000 people observed for 4 years would yield 4,000 person-years.

Overdiagnosis

Diagnosis of a disease or condition by screening that would not have been detected during the lifespan of the individual without screening.

Period effects

In statistical modelling of temporal trends of a disease, period effects are attributed to causes linked to calendar year, rather than age or year of birth.

The natural history of Barrett's oesophagus

Results from surveillance cohorts indicate that most individuals with Barrett's oesophagus do not develop oesophageal adenocarcinoma during endoscopic follow-up^{16–21}. Meta-analyses estimate the incidence of oesophageal adenocarcinoma among individuals with Barrett's oesophagus to be 6–7 per 1000 person-years^{22,23}, and oesophageal adenocarcinoma is an uncommon cause of death in people with Barrett's oesophagus^{24–27}. Furthermore, despite endoscopic detection and surveillance of Barrett's oesophagus, the vast majority of oesophageal adenocarcinomas arise in patients who have no prior diagnosis of Barrett's oesophagus^{28–31}. Therefore, the paradox of current clinical management of Barrett's oesophagus — underdiagnosis of life-threatening early disease and overdiagnosis of early benign changes that will not affect the lifespan of the individual (FIG. 2) — is similar to many other premalignant or malignant diagnoses that follow indolent courses, including those of the prostate, lung, thyroid, breast and kidney^{32–35}.

Epidemiology and aetiology

Oesophageal adenocarcinoma. The ultimate public health importance of Barrett's oesophagus lies in its association with oesophageal adenocarcinoma, the incidence of which has risen substantially in the United States, Western Europe, Australia and other developed countries over the past four decades, with little sign of abating^{6,36,37}. There is disquieting evidence for an increasing incidence of oesophageal adenocarcinoma in some Asian populations, such as those residing in Singapore³⁸, Japan³⁹ and Iran⁴⁰, where the disease has previously been uncommon, although this trend is not evident in other countries^{41,42}. In the United States, incidence is highest in Caucasian men, in whom it is around eight times greater than in Caucasian women and five times greater than in African-American men. However, substantial increases have been recorded for every group, with the result that in the United States oesophageal adenocarcinoma became the most common histological type of oesophageal cancer in the late 1990s⁶. Mortality remains high, and most patients with oesophageal adenocarcinoma survive less than 1 year after diagnosis⁴³.

Much has been learned about the aetiology of oesophageal adenocarcinoma from epidemiological studies over the past two decades. Symptomatic gastroesophageal reflux disease is the strongest and best understood risk factor. The largest population-based case-control studies have all observed fourfold or higher reported relative risks for those with the most frequent symptoms^{44–48}. It is important to note, however, that symptomatic gastroesophageal reflux disease is infrequent or absent in 40–48% of people who develop oesophageal adenocarcinoma^{44,45}.

Obesity, as measured by body mass index (BMI), also clearly increases the risk of oesophageal adenocarcinoma. This has been observed in both case-control and cohort studies^{6,46–57}. Two recent meta-analyses have estimated relative risks for developing cancer of between 2.4 and 2.8 for those with a BMI >30 kg per m² (defined as obese) and between 1.5 and 1.8 for those considered overweight (BMI = 25.0–29.9 kg per m²)^{58,59}. The importance of this relationship is magnified by the alarming increase in obesity observed in many developed countries⁶⁰. For example, on the basis of 2003–2004 National Health And Nutrition Examination Survey (NHANES) data, more than 32% of adults in the United States are obese, along with 17% of children and adolescents⁶¹. These figures represent substantial increases over a 6 year period. Similar prevalence and trends in obesity have been observed in Australia and elsewhere⁶². Cancer incidence modelling has confirmed the importance of period effects in the epidemiology of oesophageal adenocarcinoma and suggests that they are consistent with obesity trends⁶³. Preliminary evidence suggests a pattern of interaction between gastroesophageal reflux disease and obesity, such that obese people with frequent symptoms of gastroesophageal reflux disease had substantially higher oesophageal adenocarcinoma risk (odds ratio (OR) = 16.5; 95% confidence interval (CI) = 8.9–30.6) than people with obesity but no reflux (OR = 2.2; 95% CI = 1.1–4.3) or reflux but no obesity (OR = 5.6; 95% CI = 2.8–11.3) compared with people with a healthy BMI and no reflux symptoms⁴⁶.

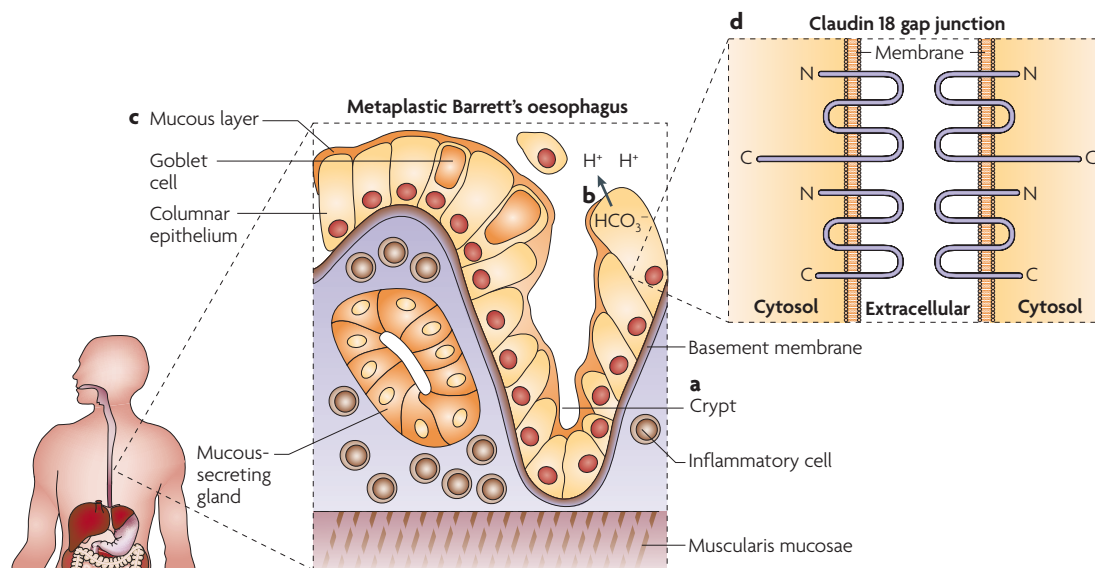


Figure 1 | Barrett's specialized intestinal metaplasia and mucosal defence. **a** | Specialized intestinal metaplasia is a well differentiated epithelium with crypt architecture in which putative stem cells residing at the base give rise to proliferating transient amplifying cells and differentiated cells that are sloughed into the lumen. This architecture has been proposed to be tumour suppressive because mutations in transient amplifying or differentiated non-stem cells would be shed from the body before they could accumulate the serial mutations that lead to cancer¹⁰. **b** | The intestinal metaplasia also secretes anions, including bicarbonate, at levels more than fivefold greater than oesophageal squamous epithelium¹¹. **c** | Specialized intestinal metaplasia, including surface columnar epithelial cells, secretes thick adherent mucus not present in normal squamous oesophageal cells¹². Ultrastructural studies have shown that mucus secretion can be disrupted in Barrett's oesophagus at increased risk of progression to oesophageal adenocarcinoma, including those with evidence of chromosomal instability and aneuploidy²¹⁴. **d** | Barrett's oesophagus has claudin 18 tight junctions that provide greater protection against acid permeation than the claudin 18-deficient tight junctions of the oesophageal squamous epithelium¹³. Barrett's oesophagus overexpresses genes involved in mucosal defence and repair¹⁴, and Barrett's oesophageal cells maintain physiological intracellular pH following prolonged and repeated reflux exposure¹⁵ (not shown).

Additional, but more modest, risk factors for oesophageal adenocarcinoma include cigarette smoking, which approximately doubles oesophageal adenocarcinoma risk^{46,47,49,57,64}, and a diet low in fruit and vegetables^{47,65–67}. Alcohol does not seem to have an important role in oesophageal adenocarcinoma^{68,69}. Infection with *Helicobacter pylori* has been linked to reduced oesophageal adenocarcinoma risk in many studies^{70–72}; the underlying mechanisms are not clear, although reduction in acid reflux in association with gastric atrophy is thought to be important⁷³.

On the basis of data from a large multi-centre US study, it is estimated that the four major risk factors — obesity (as measured by BMI), cigarette smoking, gastroesophageal reflux disease and a diet low in fruit and vegetables — individually account for 41%, 40%, 30% and 15% of cases in the US population, respectively, and collectively account for 79% (95% CI = 66–87%) of cases⁷⁴.

Barrett's oesophagus. In contrast to oesophageal adenocarcinoma, the incidence and prevalence of Barrett's oesophagus are not known with precision. Probably the most accurate population estimates of the prevalence of Barrett's oesophagus in developed countries come from a random sample of 3,000 adults in two communities in Sweden who underwent endoscopy with biopsy: Barrett's oesophagus was detected in 1.6% of those studied⁷⁵. Importantly, the prevalence of Barrett's oesophagus

among people reporting reflux symptoms (2.3%) was only modestly and nonsignificantly greater than those without such symptoms (1.2%). Remarkably similar findings were reported from an endoscopic study of 1,033 adults from two Italian villages: 1.3% were found to have Barrett's oesophagus⁷⁶. Again, reflux symptoms were a poor predictor of Barrett's oesophagus as 46.2% of Barrett's oesophagus cases did not report such symptoms.

Even in countries in which increases in oesophageal adenocarcinoma incidence have not yet been documented, such as South Korea, it seems that Barrett's oesophagus might be increasingly common⁷⁷. For example, among 992 consecutive upper endoscopies at four university hospitals in South Korea, 3.6% of individuals had histologically proved Barrett's oesophagus⁷⁷. Prevalence of risk factors for Barrett's oesophagus, such as gastroesophageal reflux disease and obesity, also seem to be increasing in some Asian countries^{38,78,79}.

Further understanding of the effects of obesity on oesophageal adenocarcinoma must largely rely on studies of precursors, such as Barrett's oesophagus, as cancer case-control studies and retrospective cohort studies are typically unable to accurately assess characteristics such as percentage of body fat and fat deposition. A cross-sectional analysis of baseline data from a cohort study of Barrett's oesophagus was among the first to suggest that the location of fat deposition was more important than weight in predicting risk⁸⁰. Recent results from

p-trend

A statistical test to determine whether an association between an exposure and a disease is consistent with a monotonic relationship.

Manometry

A test to measure electrical and motor activity in the stomach.

case-control studies of new cases of Barrett's oesophagus strongly support the idea that abdominal adiposity, rather than BMI, might be the defining characteristic that places people at increased risk of Barrett's oesophagus, and presumably oesophageal adenocarcinoma^{81,82}. For example, in a community clinic-based case-control study of people with newly diagnosed Barrett's oesophagus compared with a matched sample from the general population, people in high categories of waist-to-hip ratio (0.90 or greater for men, 0.85 or greater for women) experienced a 4.1-fold increase in risk (95% CI = 1.7–10.0; *p*-trend = 0.003), whereas no increase was observed for increasing BMI after mutual adjustment. Similar observations were reported from a population-based case-control study of Barrett's oesophagus⁸², and a case-control study nested in a large cohort in which abdominal diameter data were available⁵⁶. Supportive findings were observed in a small clinical study (*n* = 36 cases), in which visceral fat was assessed using computerized tomography (CT) scans; in models that included data for both visceral fat levels and BMI, visceral fat levels explained most of the association with risk of Barrett's oesophagus⁸³. As overweight men tend to have more visceral fat than overweight women, these studies suggest a possible explanation for the marked preponderance of men with oesophageal adenocarcinoma and Barrett's oesophagus.

It has been hypothesized that abdominal obesity might increase the risk of Barrett's oesophagus and oesophageal adenocarcinoma primarily by promoting reflux through increasing intra-gastric pressure⁸⁴. However, direct evidence for this pathway is surprisingly weak. For example, a cross-sectional hospital study using manometry observed a correlation coefficient of only 0.11 (*p* = 0.05), relating gastric pressure to BMI or waist circumference⁸⁵. Other observations suggest moderate correlations between gastroesophageal reflux disease symptoms and BMI in the United States but not in Europe⁸⁶. In one of the first studies investigating possible mediators of the obesity-Barrett's oesophagus-oesophageal

adenocarcinoma relationship, Kendall *et al.*⁸⁷ reported that high serum leptin, a hormone produced by visceral fat that might promote carcinogenesis by mitogenic and angiogenic means, was associated with an increased risk of Barrett's oesophagus, particularly among males⁸⁷. In addition to altering levels of adipokines, such as leptin and adiponectin, obesity can increase concentrations of bioavailable insulin-like growth factor 1 (IGF1) and insulin, growth factors that can directly promote cellular proliferation and reduce apoptosis, as well as affect downstream signalling pathways involved in cell growth and proliferation⁸⁸.

The strength of the relationship between cigarette smoking and Barrett's oesophagus is less clear than for oesophageal adenocarcinoma, with most^{89,90} but not all^{47,91} studies observing a modest increase in risk among current smokers. Similar to oesophageal adenocarcinoma, risk of Barrett's oesophagus seems to be moderately decreased with an increasing intake of fruit and vegetables^{92,93}.

Chronic inflammation. As described in BOX 1, one common aspect among the major risk factors for Barrett's oesophagus and oesophageal adenocarcinoma is the promotion of chronic inflammation, both in the oesophageal epithelium and systemically. It has been hypothesized that telomere length in leukocytes of people with Barrett's oesophagus might serve as an integrative measure of a person's long-term history of inflammation and oxidative damage, as factors such as insulin resistance, obesity and smoking have been shown to reduce telomere length^{94–96}. Longitudinal analysis of baseline blood samples in a Barrett's oesophagus cohort revealed shorter telomere length was associated with increased risk of progression to oesophageal adenocarcinoma (adjusted hazard ratio comparing extreme quartiles: 3.45; 95% CI = 1.35–8.78)⁹⁴. These observations were replicated in a case-control study that found overall telomere length, as well as 17p and 12q telomere lengths, but not 11q and 2p telomere lengths, were associated with increased oesophageal adenocarcinoma risk⁹⁷. These results suggest the importance of chronic systemic inflammation in the development of Barrett's oesophagus and oesophageal adenocarcinoma and raise the possibility that telomere length may be a useful component to a biomarker panel designed to stratify risk in people with Barrett's oesophagus.

Host susceptibility. A genetic component to the development of gastroesophageal reflux disease, Barrett's oesophagus and oesophageal adenocarcinoma has long been suspected on the basis of case reports, familial clusters and clinical series^{98,99}. For example, a family from the United Kingdom has been described that includes a male index case with oesophageal adenocarcinoma, three brothers with oesophageal adenocarcinoma or high-grade dysplasia in Barrett's oesophagus, and six children with Barrett's oesophagus¹⁰⁰. Similarly, a family of three generations comprising 24 individuals in Spain has been described, in which 6 developed oesophageal adenocarcinoma, 4 Barrett's oesophagus and 6 gastroesophageal reflux disease¹⁰¹. Two well-designed twin studies of gastroesophageal reflux disease also indicated

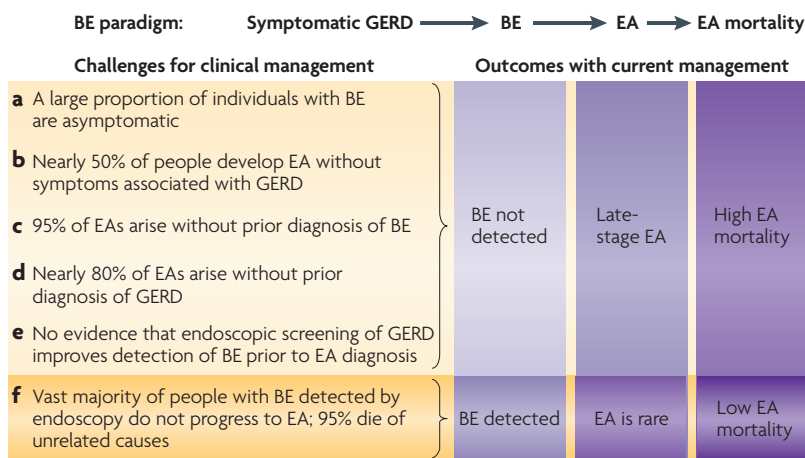
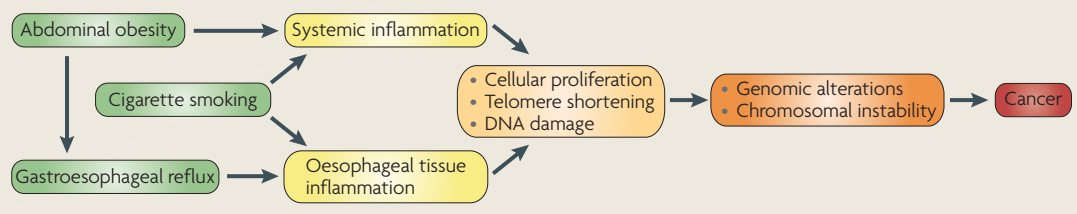


Figure 2 | The paradox of Barrett's oesophagus. Recent research has identified many factors that contribute to underdiagnosis of life-threatening early oesophageal adenocarcinoma (a–e) and overdiagnosis of benign Barrett's oesophagus that will follow an indolent course for the lifetime of the individual (f). BE, Barrett's oesophagus; EA, oesophageal adenocarcinoma; GERD, gastroesophageal reflux disease.

Box 1 | Inflammation and oesophageal adenocarcinoma

Chronic inflammation seems to have a central role in the development of oesophageal adenocarcinoma and its precursor lesions (see the figure). Epidemiological studies have identified three major risk factors — abdominal obesity (visceral fat), gastroesophageal reflux and cigarette smoking — as key driving forces for this cancer⁷⁴. The refluxate contains numerous substances in addition to gastric acid, including bile salts, pancreatic enzymes, and ingested foods and their metabolites, which can cause acute and chronic inflammation of the oesophageal epithelium with resulting oxidative stress^{195–197}. Abdominal obesity, in addition to promoting gastroesophageal reflux, is increasingly being recognized as causing a state of low-level systemic inflammation, characterized by increased plasma levels of pro-inflammatory cytokines and receptors, such as interleukin-6 (IL-6), tumour necrosis factor- α (TNF α) and TNF α receptor 2, C-reactive protein and leptin^{60,198}. In addition, cigarette smoking can cause inflammation both systemically and in the oesophageal epithelium in response to swallowed smoking products. In turn, a chronic state of systemic and localized inflammation and oxidative stress promotes DNA damage, cellular proliferation and telomere shortening, which can increase the risk of developing clones containing small- and large-scale genomic alterations, eventually leading to widespread chromosomal instability and oesophageal adenocarcinoma^{199,200}.



a heritability of 30–40%, lending further support for genetic susceptibility in the oesophageal adenocarcinoma disease process^{102,103}.

Larger studies also suggest a genetic component to oesophageal adenocarcinoma and its precursors^{104,105}. For example, familial Barrett's oesophagus was confirmed in 7.3% of people presenting with Barrett's oesophagus or oesophageal adenocarcinoma¹⁰⁶, which is higher than would be expected on the basis of population surveys^{75,76}. A higher frequency of a positive family history of Barrett's oesophagus or oesophageal adenocarcinoma among cases with these conditions (24%) compared with gastroesophageal reflux disease cases without Barrett's oesophagus (5%) has also been observed¹⁰⁷. In clinical practice, a complete family history is now recommended for physicians seeing patients with Barrett's oesophagus and oesophageal adenocarcinoma¹⁰⁸, and linkage studies are currently being undertaken to better understand the inheritance of these conditions^{109,110}.

Increasing numbers of studies have used a candidate gene approach to identify gene variants in pathways such as DNA repair, xenobiotic metabolism and inflammation that might alter the risk of developing Barrett's oesophagus or oesophageal adenocarcinoma^{110–118}. For example, a population-based study found that population heterogeneity for alcohol metabolism might have masked an increased risk with increased alcohol intake¹¹¹. Among drinkers, intermediate metabolizers had a two-fold increase in risk of oesophageal adenocarcinoma and gastric cardia adenocarcinomas, although fast metabolizers (homozygous for variant alcohol dehydrogenase 3) had a fourfold increased risk (OR = 4.3; 95% CI = 1.1–11.2). In another population-based study, relative risk of oesophageal adenocarcinoma was examined in relation to five single nucleotide polymorphisms in the DNA repair gene *MGMT*. Among people reporting frequent episodes of gastroesophageal reflux disease, a substantially increased relative risk was observed for those

homozygous for the minor allele at the intronic locus rs12268840 (OR = 15.5; 95% CI = 5.8–42), although the association of the variant with altered expression or enzyme activity is unclear¹¹⁵. Another study examined variants in the NAD(P)H:quinone oxidoreductase 1 (*NQO1*) gene, which encodes a detoxifying enzyme of common dietary compounds. Those with the TT genotype were less common than expected in Barrett's oesophagus and oesophageal adenocarcinoma cases, yielding a 4.5-fold decreased risk of developing Barrett's oesophagus ($p = 0.01$) and a 6.2-fold decreased risk of oesophageal adenocarcinoma ($p = 0.04$), and suggesting that the *NQO1* TT genotype may offer protection from reflux complications¹¹⁹.

COX2 (also known as *PTGS2*) is of particular interest as it encodes an inducible form of cyclooxygenase that can be expressed at increased levels in Barrett's oesophagus, oesophageal adenocarcinoma, and several other cancers and their precursors. Cyclooxygenase has a central role in inflammation and potentially carcinogenesis through the production of prostaglandins, which have several neoplastic properties¹²⁰. Variants in the promoter region of *COX2* have been observed to significantly increase the risk of oesophageal adenocarcinoma^{121,122}; this is intriguing, given the number of observational studies indicating a preventive effect of non-steroidal anti-inflammatory drugs (NSAIDs) in the development of oesophageal adenocarcinoma^{123–127} (discussed below).

In a cohort study of Barrett's oesophagus, bleomycin sensitivity was assessed in baseline peripheral blood lymphocytes. Bleomycin-sensitive patients were at an increased risk of developing aneuploid cells (adjusted hazard ratio (HR) 3.71; 95% CI 1.44–9.53) and non-significantly greater risk of oesophageal adenocarcinoma (adjusted HR 1.63; 95% CI 0.71–3.75)¹²⁸. Trends for both oesophageal adenocarcinoma ($p < 0.001$) and aneuploidy ($p < 0.005$) were particularly strong among patients with 17p loss of heterozygosity (LOH) involving *TP53*.

Longitudinal studies

Observational studies in which the disease (and perhaps exposure) experience of a group of individuals is observed over multiple time points.

Chromosomal instability

An increased rate of gain or loss of whole chromosomes or large proportions of chromosomes.

Together, the above results suggest the importance of taking into account genetic background when evaluating risk and preventive factors in the development of Barrett's oesophagus and oesophageal adenocarcinoma and vice versa. However, they all require replication and further functional studies before this information can be used in a clinical setting. Results from ongoing genome-wide association studies of Barrett's oesophagus and oesophageal adenocarcinoma will probably add new loci of interest for more directed study.

Neoplastic progression in Barrett's oesophagus

One of the fundamental goals of translational research in Barrett's oesophagus is to distinguish the small number of individuals who progress to oesophageal adenocarcinoma from the majority who do not. Currently, periodic endoscopic biopsies with histological assessment of dysplasia are used to assess the risk of progression to oesophageal adenocarcinoma in patients with Barrett's oesophagus. Dysplasia is also frequently used as a surrogate end point for oesophageal adenocarcinoma in research studies. However, this approach poses substantial challenges for both patient care and research (BOX 2). Formal statistical criteria for evaluating surrogate biomarkers were developed two decades ago¹²⁹. Although some surrogates with lower standards can be used for intermediate studies or biological pathway analysis¹³⁰, surrogate markers for studies that intend to contribute to the evidence base for clinical policy need to accurately represent the true end point, oesophageal adenocarcinoma. Such markers need to be in key causal pathways to oesophageal adenocarcinoma, have substantial predictive power to distinguish

between those who will and will not develop oesophageal adenocarcinoma, and be easily and objectively measured. As neither high-grade dysplasia nor any other grade of dysplasia in Barrett's oesophagus has been demonstrated to be a valid surrogate for oesophageal adenocarcinoma, this Review focuses on well-designed longitudinal studies of neoplastic progression that have a definitive oesophageal adenocarcinoma end point.

In 1976, Nowell advanced the hypothesis that "Acquired genetic lability permits stepwise selection of variant sublines and underlies tumour progression" (REF. 131). Data from genomic^{132–134}, transcriptomic^{135–138} and proteomic^{138,139–141} studies have revealed the complexity of changes that develop during neoplastic evolution to oesophageal adenocarcinoma, including genome-wide chromosomal instability, disruption of regulatory pathways and dynamic clonal evolution (BOX 3).

Genomic instability. Genomic instability seems to be a fundamental property of neoplastic progression that develops before the onset of cancer. Chromosome instability is the most common source of genomic instability in human cancers, and it has been best evaluated in colon cancer, in which it constitutes around 85% of the genetic instability leading to cancer compared with microsatellite instability, which comprises the remaining 15%¹⁴². A large body of evidence now suggests that most oesophageal adenocarcinomas arise in association with a process of gain or loss of whole chromosomes or large portions of chromosomes, as detected by DNA content flow cytometry, cytogenetics, LOH, comparative genomic hybridization (CGH), array CGH and single nucleotide polymorphism (SNP) arrays^{132–134,143–145}. A recent Human Hap300 SNP array study of 23 oesophageal adenocarcinomas reported an average of 97 copy number changes (range 23–208) per cancer that ranged in size from small homozygous deletions to large chromosome regions¹³². Copy gain, loss and copy neutral LOH averaged 13 Mb, 18 Mb and 23 Mb, respectively. All tumours had LOH involving most of chromosome 17p, and alterations were identified in established tumour suppressor genes and oncogenes such as *CDKN2A*, *TP53*, *FHIT* and *MYC*, as well as new candidate gene regions. These results indicate the complexity of genomic changes in oesophageal adenocarcinoma and suggest that there will be both opportunities and challenges for risk stratification, cancer prevention and early detection.

Chromosome abnormalities have been detected in Barrett's oesophagus epithelium adjacent to oesophageal adenocarcinomas, and distributions of cell populations with chromosome abnormalities have been reported at the scales of individual cells, crypts and biopsies in Barrett's oesophagus epithelia^{146–149}. Spatial data at the level of biopsies in the Barrett's oesophagus epithelia led to the hypothesis that 9p LOH (as well as methylation and mutation of *CDKN2A*) are early events in Barrett's oesophagus that preceded 17p LOH and *TP53* mutation, and later DNA content tetraploidy and aneuploidy^{146,148}. In a long-term prospective study of 243 patients with Barrett's oesophagus using oesophageal adenocarcinoma as an outcome¹²³, baseline biopsies were evaluated for the

Box 2 | Challenges to histology-guided clinical care

- Assessment of dysplasia is subjective with substantial observer variation in diagnosis between pathologists^{201,202}.
- Large numbers of biopsies are required to reduce sampling error^{168,203}.
- High-grade dysplasia is highly heterogeneous with regard to progression to oesophageal adenocarcinoma, and rates of progression vary substantially in different studies with reported 5-year cumulative incidences of oesophageal adenocarcinoma ranging from less than 10% to 59%^{17,20}.
- Low-grade dysplasia has a low rate of progression to oesophageal adenocarcinoma, non-robust reproducibility and is frequently not detected in subsequent endoscopies^{16–18,20,202,204–206}.
- Reports of increased progression from low-grade dysplasia to high-grade dysplasia as a surrogate end point for oesophageal adenocarcinoma²⁰⁷ might be confounded by diagnostic misclassification^{201,202}, sampling²⁰⁸, biological heterogeneity or combinations of these factors.
- The lack of reproducible diagnostic classification^{201,202} confounds comparison of results from different centres.
- Use of dysplasia as a surrogate marker for oesophageal adenocarcinoma in molecular or imaging research for improved risk stratification can hardwire the limitations of the dysplasia classification system into the molecular and imaging markers^{153,154}.
- The treatment of surrogate end points for oesophageal adenocarcinoma, such as low- or high-grade dysplasia, might not be associated with decreased incidence of advanced oesophageal adenocarcinomas or reduction in mortality^{190,191}.
- Research on quantitative assessment of dysplasia^{208,209} and consensus interpretations²¹⁰ is being carried out to improve histological classification, but some results are inconsistent and no studies have yet demonstrated the sensitivity and specificity expected of a practical diagnostic test.

Box 3 | Opportunities for risk stratification, prevention and early detection

The complex patterns of chromosome instability and mutations, combined with the disruption of regulatory pathways, clonal evolution and generation of variants create challenges for treatment of advanced oesophageal adenocarcinoma (see the table). Rapidly advancing technology creates opportunities to measure fundamental, widely generalizable biomarkers of progression for risk stratification, early detection and prevention. For example, the presence or rate of chromosome instability can be measured on high-density, genome-wide platforms and might be a fundamental biomarker that captures the complexity of neoplastic progression in Barrett's oesophagus and many other conditions. Assessment of the disruption of regulatory pathways at the expression or protein levels could integrate genomic, epigenetic and environmental influences on progression, and expression profiles have received regulatory approval for the selection of patients for specific therapies, as well as the identification of carcinomas of unknown primary origin^{212,213}. Measures of evolution, including clonal expansion and generation of diversity, might also be fundamental biomarkers of progression that could be applicable to many conditions in addition to Barrett's oesophagus. The complexity of these abnormalities seems to be lower in premalignant stages of Barrett's oesophagus than in oesophageal adenocarcinoma, which could facilitate development of diagnostic tests, although it is likely that no single measurement will prove sufficient for cancer control. Early events found in high frequency in Barrett's oesophagus are unlikely to be useful as biomarkers of risk of progression to oesophageal adenocarcinoma because the natural history of Barrett's oesophagus indicates that progression to, and death from, oesophageal adenocarcinoma are rare events. High frequency early events in Barrett's oesophagus could be part of the mucosal defence of Barrett's oesophagus as an adaptation to chronic gastroesophageal reflux disease (FIG. 1); neutral alterations in regions susceptible to chromosome damage that undergo expansion as hitchhikers (passengers) on early selected genetic or epigenetic drivers; or necessary, but not sufficient for progression to oesophageal adenocarcinoma.

Fundamental properties of neoplastic progression	Measures of alterations	Challenges for translation
Genomic instability, chromosomal alterations, chromosome instability, microsatellite instability and mutations	Aneuploidy ^{134,143,144} , copy number and LOH ^{132,133,145} and microsatellite alterations ¹⁴³	High-dimensional complexity of genomic alterations and random neutral events
Disruption of regulatory pathways	Transcription profiles ^{135–138} , methylation patterns ^{152,155–157,211} , proteomics ^{139–141} , cellular proliferation ¹⁶⁶ and cell cycle abnormalities ^{161–164}	Redundancy and dynamic adaptation of networks
Changes in clonal evolutionary dynamics	Clonal expansion ¹⁴⁶ , clone size ¹⁵⁹ , genetic divergence ¹⁶⁰ , diversity and generation of variants ^{147,160}	Heterogeneity, changes in rates and selection of variants
LOH, loss of heterozygosity		

presence of 9p LOH, 17p LOH, DNA content abnormalities (tetraploidy and aneuploidy), *TP53* mutation and *CDKN2A* mutation and methylation. After 10 years of follow-up, all biomarkers significantly contributed to the risk of oesophageal adenocarcinoma in a univariate analysis, with the exceptions of *CDKN2A* methylation and mutation. The chromosome instability panel of 9p LOH, 17p LOH and DNA content abnormalities was the best predictor of oesophageal adenocarcinoma (relative risk = 38.7; 95% CI = 10.8–138.5; $p < 0.001$). The 5 year cumulative incidence of oesophageal adenocarcinoma was 79.1% in individuals with 9p LOH, 17p LOH and a DNA content abnormality at baseline, whereas those with neither LOH nor DNA content abnormalities at baseline had a 0% cumulative incidence of oesophageal adenocarcinoma almost 8 years after the baseline endoscopy.

Although this study established that measures of chromosome instability can distinguish individuals at high and low risk for progression to oesophageal adenocarcinoma, it used a constellation of technologies that are difficult to carry out outside of research centres. Two recent studies have reported that SNP and bacterial artificial chromosome arrays have high sensitivity and specificity to detect DNA content aneuploidy, and SNP arrays provide a single platform to assess chromosome instability, including copy change and LOH^{133,150}. Patients whose Barrett's oesophagus biopsies contained copy number alterations involving more

than 70 Mb of the genome also had an increased risk of progressing to DNA content abnormalities or oesophageal adenocarcinoma during follow-up¹⁵⁰.

Therefore, substantial evidence indicates that chromosome instability is strongly associated with progression from Barrett's oesophagus to oesophageal adenocarcinoma. Rapid advances in DNA technology provide opportunities for translation of 9p, 17p and DNA content abnormalities using clinically compatible platforms such as Pyrosequencing for LOH and fluorescent *in situ* hybridization for copy number alterations^{149,151}. SNP arrays allow the assessment of LOH, copy number and aneuploidy on a common platform in Barrett's oesophagus and oesophageal adenocarcinoma, demonstrating that chromosome instability was common in people with Barrett's oesophagus that had progressed to oesophageal adenocarcinoma as well as in advanced oesophageal adenocarcinomas¹³³. Small interstitial deletions are frequently observed in people with early stages of Barrett's oesophagus who did not undergo progression to oesophageal adenocarcinoma^{133,145}. These small deletions do not meet the definition of chromosomal instability^{133,142}, and their roles in Barrett's oesophagus are not yet clear. They might be selected during the adaptation for mucosal defence in gastroesophageal reflux disease (FIG. 1), neutral alterations in regions susceptible to chromosome damage that expand as hitchhikers

Interstitial deletion

A deletion of variable size that does not involve the terminal parts of a chromosome.

CpG island

The CG island is a short stretch of DNA in which the frequency of the CG sequence is higher than in other regions. The p indicates that C and G are connected by a phosphodiester bond.

Shannon Index

Combines both the number and relative abundance of clones. It is also known as the information content or entropy.

(passengers), or necessary but not sufficient for oesophageal adenocarcinoma (BOX 3)¹³³. Regardless, alterations in these small regions are far too common in early stages to be sufficient for the development of oesophageal adenocarcinoma, as shown by the low rate of progression from Barrett's oesophagus to oesophageal adenocarcinoma^{22,23}. Microsatellite instability is another potential source of genome-wide instability in the development of oesophageal adenocarcinoma, although it seems to be much less common than chromosome instability perhaps accounting for 5% of oesophageal adenocarcinomas¹⁴³.

Epigenetic changes in Barrett's oesophagus and oesophageal adenocarcinoma. There has been recent interest in epigenetic mechanisms, especially DNA methylation, in the development of oesophageal adenocarcinoma, and the promoter regions of several dozen genes have been evaluated using candidate genes identified in other cancers¹⁵². A few longitudinal studies of epigenetic abnormalities have also been reported, using a mixture of surrogate dysplasia and oesophageal adenocarcinoma end points and based on promoter regions of a small number of genes^{153,154}. Recent studies have used unbiased scans of the genome to investigate DNA methylation in different tissue types and in cancers^{155,156}, with one study of colon cancer reporting that most methylation changes were not in promoters or CpG islands¹⁵⁷. Combining recent advances in genome-wide screens with spatial scale experiments is likely to lead to a better understanding of the roles of methylation in tissue maintenance and neoplasia in Barrett's oesophagus and oesophageal adenocarcinoma^{155–157}.

Clonal evolution and neoplastic progression in Barrett's oesophagus. Although Nowell's theory of clonal evolution is generally accepted^{131,158}, few studies have addressed clonal evolutionary dynamics, which might be fundamental biomarkers of cancer risk applicable to a large number of neoplasms. Three studies carried out on overlapping cohort sets have evaluated evolutionary parameters in neoplastic progression in Barrett's oesophagus. A spatial study reported that *CDKN2A* mutation and methylation, 9p LOH, *TP53* mutations and 17p LOH were all highly selected (drivers) for clonal expansion¹⁴⁶. By contrast, all microsatellite shifts and other LOH events behaved as neutral mutations. In some cases, neutral mutations underwent large clonal expansions, but these expansions could typically be explained by co-expansion as hitchhikers (passengers) on a clonal expansion driven by a known selective mutation. A second study evaluated the relative importance of clonal expansion and genetic instability and reported that the sizes of clones with 17p LOH or DNA content tetraploidy and aneuploidy increased the risk of progression from Barrett's oesophagus to oesophageal adenocarcinoma¹⁵⁹. Sizes of clones with *CDKN2A* abnormalities were not significant oesophageal adenocarcinoma risk factors when 17p LOH was included in the model, suggesting that the expansion of a genetically unstable clone increases the risk of progression of Barrett's oesophagus to oesophageal adenocarcinoma. In a third study, increased clonal diversity, assessed by number of clones, Shannon Index and mean pairwise genetic divergence between flow

cytometry-enriched fractions of Barrett's oesophagus biopsies, was associated with increased risk of progression to oesophageal adenocarcinoma even when 17p LOH and DNA content abnormalities were included in the model¹⁶⁰. It is not yet clear whether measures of diversity in crypts or single cells are associated with an increased risk of progression to oesophageal adenocarcinoma.

Another interesting study observed marked genetic diversity at the crypt level in Barrett's oesophagus after dissecting individual crypts and evaluating them for LOH involving *APC* (5q), *CDKN2A* (9p) and *TP53* (17p), as well as mutations in *CDKN2A* and *TP53* (REF. 147). In one patient, a non-coding *CDKN2A* mutation was present in both a squamous oesophageal duct and metaplastic Barrett's oesophagus, suggesting a ductal origin of Barrett's oesophagus. Such careful attention to spatial scale advances our understanding of levels of diversity in Barrett's oesophagus that might be important in evolution of oesophageal adenocarcinoma or the development of treatment resistance.

Cellular proliferation. Abnormal proliferation and cell cycle intervals have long been known to be associated with Barrett's oesophagus, and increased proliferative indices seem to be a physiological adaptation to reflux in some studies¹⁶¹. In a small study, expression of minichromosome maintenance proteins was reported to be associated with an increased risk of progression to oesophageal adenocarcinoma¹⁶². In a recent case-control study of 29 patients who progressed to oesophageal adenocarcinoma and 6 who progressed to the surrogate end point, high-grade dysplasia, p53 expression (as assessed by immunohistochemistry) was associated with an increased risk of progression (OR = 11.7; 95% CI = 1.93–71.4), but expression of *cyclin D1*, *COX2* and *β-catenin* was not¹⁶³. However, an earlier nested case-control study of 12 individuals who progressed to oesophageal adenocarcinoma from a cohort of 307 people with Barrett's oesophagus reported that p53 immunopositivity was not associated with a significant risk of progression (OR = 2.99; 95% CI = 0.57–15.76) and that cyclin D1 expression was associated with progression (OR = 6.85; 95% CI = 1.57–29.91)¹⁶⁴. The reasons for the discrepancies are unknown and population differences, sample size and, in the case of p53, clone size, type of *TP53* mutation and other somatic genetic changes in the evolving Barrett's segment could all contribute^{159,165}.

A cohort study of 362 patients with mean follow-up of 6.3 years and a total of 1,752 person-years follow-up evaluated diploid cell proliferation and cell cycle interval fractions (G1, S and 4N) assessed at the baseline endoscopy as predictors of progression to oesophageal adenocarcinoma¹⁶⁶. Higher total proliferative or G1 fractions were not associated with progression to oesophageal adenocarcinoma; increased S phase fractions were marginally associated with progression ($p = 0.03$); and increased 4N fractions, which were highly associated with biallelic inactivation of *TP53*, were significantly associated with progression ($p < 0.0001$). Therefore, some proliferative changes seem to be adaptive changes to reflux, whereas others are the consequence of inactivation of tumour suppressors. Those that are highly

associated with inactivation of *TP53*, such as 4N fractions, are strong and significant predictors of progression to oesophageal adenocarcinoma.

Prevention and early detection

The challenge remains to reduce the incidence and mortality of oesophageal adenocarcinoma. No prevention or early detection strategy has yet conclusively been proved to reduce oesophageal adenocarcinoma or all-cause mortality in individuals with Barrett's oesophagus. Current approaches to oesophageal adenocarcinoma control are largely based on the symptomatic gastroesophageal reflux disease–Barrett's oesophagus–oesophageal adenocarcinoma paradigm, but emerging data challenge many underlying assumptions (FIGS 1,2).

The usefulness of endoscopic screening for Barrett's oesophagus and oesophageal adenocarcinoma has come into question¹⁶⁷. In 2008, the American College of Gastroenterology Guidelines withdrew recommendations for endoscopic screening of patients with gastroesophageal reflux disease¹⁶⁸, and an American Gastroenterological Association Institute technical review concluded there was no direct evidence supporting endoscopic screening for either Barrett's oesophagus or oesophageal adenocarcinoma in individuals with gastroesophageal reflux disease¹⁶⁹. An alternative research approach would be to develop a general population risk model, taking advantage of existing data from consortia of observational and intervention studies, as has previously been suggested for oesophageal adenocarcinoma¹⁷⁰ (BOX 4). Such a model could be used to guide health policy and provide education about when to consult a medical provider (see REF. 171 for more information). Other measures derived from consortia data, such as *H. pylori* status, anthropometric measures and family history, could be used to develop a primary care risk model to facilitate risk stratification and guide referral (BOX 4). Recent research has also identified promising leads for assessing biomarkers in the primary care setting, including blood tests⁹⁴ and non-endoscopic oesophageal cytology¹⁷², which could include biomarkers that identify people with Barrett's oesophagus who are at a high risk for progression to oesophageal adenocarcinoma. High sensitivity and especially specificity of the primary care risk model, perhaps as afforded by such biomarkers, will be key in developing programmes of prevention and early detection that have a substantial affect on oesophageal adenocarcinoma incidence and mortality.

There are data to support the effectiveness of endoscopic biopsy surveillance for early detection of oesophageal adenocarcinoma. Several retrospective studies have compared oesophageal adenocarcinomas arising in individuals who have been in a surveillance programme for Barrett's oesophagus with those with newly diagnosed oesophageal adenocarcinomas who had not been in endoscopic surveillance^{29,31,168,173–179}. Oesophageal adenocarcinomas were detected at earlier stages in the surveillance populations than those not in surveillance, and patients in surveillance generally, but not always, had significantly improved survival. However, most of these studies had small sample sizes, some had short follow-up intervals and none were randomized control trials.

The leading chemoprevention candidate for oesophageal adenocarcinoma is currently aspirin, as protective associations have been consistently reported in population-based case–control and cohort studies as well as in meta-analyses^{123,125–127,180}. Inhibition of COX2 has also been reported to decrease the incidence of oesophageal adenocarcinoma in an animal model of Barrett's oesophagus¹⁸¹. In Ireland, a population-based study of people with reflux oesophagitis, Barrett's oesophagus, oesophageal adenocarcinoma and population controls observed that the use of aspirin and other NSAIDs was associated with a significantly reduced risk of Barrett's oesophagus and oesophageal adenocarcinoma¹²⁴. Other population-based case–control studies have observed regular aspirin or other NSAID use to be associated with similar reductions in oesophageal adenocarcinoma incidence^{182,183}. A prospective cohort study of individuals with Barrett's oesophagus reported that current users of aspirin and other NSAIDs had a reduced rate for progression to oesophageal adenocarcinoma compared with never users¹²⁷. Current users also had a reduced progression to DNA content aneuploidy and tetraploidy compared with never users. Current use of aspirin and other NSAIDs has also been associated with a marked risk reduction in patients with multiple chromosome instability abnormalities at baseline: NSAID non-users had a 79% 10-year cumulative incidence of oesophageal adenocarcinoma compared with 30% for current NSAID users ($p < 0.001$)¹²³. It should be noted that one small trial of the COX2 inhibitor celecoxib evaluated changes in several surrogate end points after 48 weeks of treatment, initially reporting no difference in the proportion of biopsies with dysplasia, total surface area of Barrett's oesophagus, prostaglandin levels, *COX1* and *COX2* mRNA levels or methylation of several tumour suppressor genes¹⁸⁴. However, a subsequent analysis using more detailed data available on a subset of the trial participants found a significant decrease in total Barrett's area among those taking celecoxib¹⁸⁵. Taken together, these results suggest that the anti-inflammatory effects of aspirin and other NSAIDs might exert both early and late effects on neoplastic progression.

Proton pump inhibitors, a class of drugs that substantially reduces gastric acid production, came into widespread use in the early to mid-1990s for the treatment of symptoms of gastroesophageal reflux, among other indications. Several observational studies have examined the association between use of these drugs and surrogate end points for oesophageal adenocarcinoma, but with conflicting results. One recent retrospective cohort study examined pharmacy records to estimate the use of proton pump inhibitors in 344 individuals without any dysplasia at initial endoscopy, reporting no association with the development of any dysplasia, but a statistically significant reduction in risk of high-grade dysplasia and/or oesophageal adenocarcinoma¹⁸⁶. A potential limitation of the study, beyond the use of non-cancer end points, is the fact that more than 40% of the cohort were initially seen before proton pump inhibitors were generally available (between 1982 and 1992); therefore any difference in risk of progression over time experienced by the cohort would bias the observed association with use of proton

Box 4 | Prevention and control of oesophageal adenocarcinoma

A new strategy has been proposed (see the table) to build on research advances and overcome the limitations that are inherent in current approaches to controlling oesophageal adenocarcinoma incidence and mortality (BOX 2; FIG. 2). A key goal is to cost-effectively classify people into increasingly high-risk target populations, on the basis of comprehensive risk models using the increasing amount and sophistication of information available in each setting. Each stratum can be offered programmes of prevention and early detection appropriate for their absolute risk of developing oesophageal adenocarcinoma. A key to the success of such an approach is the substantial improvement of specificity at each stratum, probably aided by blood- and tissue-based biomarkers of risk, which will allow the identification of the large proportion of people who are unlikely to develop oesophageal adenocarcinoma, allowing them to avoid or minimize worrisome, costly and risky endoscopic surveillance and interventions. At each level of risk, research needed to create effective prevention programmes is shown in the table. As suggested by Khoury *et al.*²¹⁵, such translational research typically involves developing and validating tests, risk models and prediction tools, and implementing corresponding preventive interventions in the target population, followed by an evaluation component (not shown) to identify tools and interventions in need of improvement.

Risk of developing oesophageal adenocarcinoma	Prevention and control activities	Research needs
Extremely low	Education and health policy development for the general population	Precisely quantify independent and joint effects of the key risk factors for oesophageal adenocarcinoma, taking advantage of observational and intervention studies ⁷⁴ . Develop a general population risk model to identify the most important risk and prevention factors operating in the population ¹⁷⁰ . Develop and implement cost-effective health care policies ¹⁷¹ and education programmes to encourage healthy lifestyles in the context of low absolute risk of oesophageal adenocarcinoma and give clear guidelines for when to consult a medical provider
Very low	Primary care, involving clinical screening, education and counselling, and risk stratification and referral	Develop and validate effective clinical screening tests to aid in risk stratification. Biomarkers based on blood and other body fluids could identify <i>Helicobacter pylori</i> status ^{70–72} , telomere length ⁹⁴ and levels of inflammation and related proteins or hormones ⁸⁷ . Non-endoscopic cytology ¹⁷² could also be used to identify biomarkers associated with a high risk of developing oesophageal adenocarcinoma. Develop a primary care risk model that expands on a population model to encompass screening biomarkers and additional information available in a clinical setting, such as anthropometry ^{81,82} , family history ¹⁰⁸ , symptoms and genetic susceptibility. Create a risk prediction tool for primary care providers to facilitate patient education and counselling regarding lifestyle modification ²¹⁶ , and risk stratification and referral decisions
Low	Secondary care encompassing endoscopic screening, lifestyle-based interventions and risk stratification	Develop and validate objective and reproducible tissue-based markers for effective risk stratification ^{123,159,160,163} . Develop and validate safe interventions, such as weight loss ⁸⁶ and an improved diet, that are appropriate for a patient population at increased, but low overall risk of developing oesophageal adenocarcinoma. These must be shown to reduce the incidence of oesophageal adenocarcinoma or validated markers of risk and be consistent with common competing factors such as cardiovascular disease ^{26,217} . Develop a secondary care risk model that expands on the primary care model to encompass endoscopic and tissue-based biomarkers. Create a risk prediction tool to guide decisions regarding surveillance and interventions
Moderate	Secondary care involving surveillance, chemoprevention and risk stratification and referral	Develop and validate a cost-effective panel of interventions appropriate for people at moderate risk of developing oesophageal adenocarcinoma. In addition to lifestyle modifications, these could include chemoprevention using aspirin ^{125,180} , and other medical treatments that safely reduce the risk of developing oesophageal adenocarcinoma and/or mortality from this disease and have been validated in clinical trials. Develop and validate a cost-effective surveillance protocol ²¹⁸ and management plan based on a secondary care risk model. These must be shown in clinical trials to reduce the risk of developing oesophageal adenocarcinoma and/or mortality from this disease
High	Specialized care including medical and surgical interventions	Develop and validate medical and surgical interventions, such as ablation ^{190,192} , that are appropriate for people at a high risk of developing oesophageal adenocarcinoma. Such interventions must have been shown in clinical trials to reduce the risk of developing oesophageal adenocarcinoma and/or mortality from this disease more effectively than those measures shown to be effective in secondary care protocols

pump inhibitors. Another study examined the occurrence of regression of Barrett's oesophagus among 188 people taking proton pump inhibitors¹⁸⁷. They found no evidence of a reduction in the length of the Barrett's segment after a mean of 5.1 years of treatment. As *in vitro* studies suggest a possible antiproliferative effect of acid exposure in Barrett's cell lines, mediated through p53, clinical trials are clearly needed to address the long-term effects of proton pump inhibitors on the risk of oesophageal adenocarcinoma¹⁸⁸.

A randomized trial of aspirin and two doses of proton pump inhibitors for Barrett's oesophagus without high-grade dysplasia is currently underway in the United Kingdom that includes all cause mortality outcome and might shed additional light on the effectiveness of aspirin and proton pump inhibitors as chemopreventive agents in people with Barrett's oesophagus without high-grade dysplasia¹⁸⁹. A randomized trial of high-risk individuals might also be considered in light of evidence that aspirin and other NSAIDs also function at an advanced stage of neoplastic progression¹²³. Additional candidate preventive measures, including weight loss, increased physical activity, smoking cessation and increased intake of plant-based foods, might help reduce the incidence of oesophageal adenocarcinoma in the general population and in high-risk people defined by genetics, lifestyle or biomarkers. However, all remain to be demonstrated as effective in a prevention trial.

More aggressive approaches to prevention, including treating patients with Barrett's oesophagus with photodynamic therapy (PDT) and radiofrequency ablation (RFA) have been evaluated in multi-centre randomized trials with incomplete blinding and surrogate dysplasia primary end points¹⁹⁰⁻¹⁹². The PDT trial reported a decreased incidence of oesophageal adenocarcinoma as a secondary end point, with a nonsignificant increase in T2 and T3 oesophageal adenocarcinomas in the PDT arm, but patients who developed cancers were excluded as treatment failures and oesophageal adenocarcinoma mortality could have been underestimated^{190,191}. Adverse events, such as photosensitivity, strictures, nausea and vomiting, and pain, were also common (observed in 94% of patients). The RFA trial had only surrogate primary and secondary end points, small sample size and short post-ablation follow-up of only a few months in many patients. Although there was a decrease of borderline significance in the incidence of oesophageal adenocarcinoma among patients with high-grade dysplasia in the treatment arm during the short follow-up period ($p = 0.04$), a trial with a substantially larger sample size, longer follow-up and primary end points of oesophageal adenocarcinoma incidence and mortality is needed to validate the effect. No patient with low-grade dysplasia developed oesophageal adenocarcinoma, consistent with the known low risk, transient nature and lack of robust reproducibility of this diagnosis (BOX 2). In addition, approximately 10% of patients receiving RFA for non-nodular dysplasia had adverse events requiring additional medical care, including upper gastrointestinal bleeding, chest pain requiring hospitalization and strictures requiring dilation, compared with none in the control arm. Endoscopic mucosal resection (EMR) is frequently carried out in nodular

dysplasia for the effective selection of patients for endoscopic therapy before RFA; the combination of EMR and RFA can result in a constellation of adverse events affecting more than 20% of patients, including bleeding, oesophageal laceration, oesophageal perforation, oesophageal stricture requiring dilation, and fever and chest pain requiring hospitalization¹⁹³. Although the length of follow-up in the RFA trial was insufficient to assess the recurrence of Barrett's oesophagus after therapy, the neosquamous epithelium after ablation is prone to undergo the fate of its precursor, the native oesophageal squamous epithelium, which lacks the mucosal defences of specialized intestinal metaplasia (FIG. 1) and recurrence of Barrett's oesophagus has been reported in up to two-thirds of patients¹⁹⁴.

Conclusions and perspective

The incidence of oesophageal adenocarcinoma has risen more rapidly than any other cancer in Western countries, and there is evidence for increasing incidence in regions of Asia where the diagnosis was previously almost unknown. Current approaches for controlling oesophageal adenocarcinoma incidence and mortality are largely based on endoscopic investigation of symptomatic gastroesophageal reflux disease and histology-guided surveillance and treatment of people with Barrett's oesophagus have considerable limitations (BOX 2; FIG. 2). New oesophageal adenocarcinoma prevention strategies will be needed to overcome these limitations and decrease the current high mortality associated with oesophageal adenocarcinoma (BOX 4).

Advances have been made over the past decade in our understanding of host and environmental factors associated with oesophageal adenocarcinoma, including the role of obesity and the protective associations of aspirin and other NSAIDs. These and other factors can guide development of population risk models¹⁷⁰. Advances have also been made that can assist the development of primary care risk models, including family history, *H. pylori* testing, non-endoscopic cytology and blood tests. With rapid advances in DNA array technology, more precise and higher resolution measurements of both the constitutive genome and the evolving neoplastic genome are now possible with platforms that can be translated into the clinic setting. However, the complexity of the process of neoplastic progression suggests that no single measure is likely to be sufficient for practical clinical oesophageal adenocarcinoma risk stratification over a person's lifetime (BOX 3).

A substantial challenge remains in that no intervention, including lifestyle modification, chemoprevention and medical or surgical treatments, has yet convincingly been shown to reduce oesophageal adenocarcinoma incidence and/or mortality. Consortia with multidisciplinary expertise in population, genomic, computational, clinical and other sciences will be required to effectively address these challenges, with the goals of developing personal risk stratification based on interactions among environmental factors, the constitutive genome and the evolving neoplastic genome and delivering personalized care in the form of interventions tailored to an individual's oesophageal adenocarcinoma risk.

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Competing interests statement

The authors declare no competing financial interests.

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