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Review

Strategies for the prevention of oesophageal adenocarcinoma

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HIGHLIGHTS

- Urgent action is required to halt the dramatic rise in oesophageal adenocarcinoma.
- Aspirin and statins have demonstrated significant potential as chemopreventive agents.
- Modern endoscopic therapies (EMR and RFA) can prevent progression to malignancy.

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ABSTRACT

The incidence of oesophageal adenocarcinoma has increased by 500% over the past 30 years [1]. Improved understanding of the mechanisms of neoplastic progression provides an opportunity to reverse this trend. A thorough review of emerging strategies aiming to prevent the formation of oesophageal malignancy is presented. These include dietary modification, chemoprevention, early endoscopic identification and treatment of premalignant disease, and the potential for a non-endoscopic screening test. Oesophageal adenocarcinoma has become a major public health problem in the West and it is essential that clinicians are fully informed of risk reduction strategies so that they can be actively promoted in the community.

1. Introduction

The incidence of oesophageal adenocarcinoma is rising more rapidly than any other solid tumour in the Western world with an increase of 500% recorded over the past 30 years [1]. Despite centralisation of cancer services leading to improvements in operative mortality, overall 5 year survival remains just 10% reflecting the late presentation of oesophageal tumours [2].

There is a critical need to develop strategies to limit the occurrence of invasive adenocarcinoma either by modulation of cellular neoplastic pathways or by improvements in early detection and aggressive treatment of Barrett's-associated oesophageal dysplasia.

The development of oesophageal adenocarcinoma follows a well described sequential progression from normal squamous mucosa, to metaplasia (Barrett's oesophagus), and then low-grade and high-grade dysplasia. The recognition of glandular dysplasia as the premalignant lesion has facilitated the development of strategies to enable early detection and intervention, with the aim of preventing progression to malignancy. This approach has been successful in the setting of premalignant cervical intraepithelial neoplasia and adenomatous colonic polyps, and it is hoped could similarly significantly decrease the mortality and morbidity associated with oesophageal cancer.

This article reviews the current evidence supporting strategies to prevent the formation of oesophageal adenocarcinoma, including dietary and lifestyle factors, chemomodulation, and emerging techniques for identifying and eradicating premalignant dysplasia. The role of Barrett's surveillance is discussed, as is the potential for non-endoscopic population-based screening using promising molecular techniques.

2. Lifestyle and dietary factors

Avoidance of established oesophageal cancer risk factors and awareness of protective factors are widely endorsed and can have far-reaching health and economic benefits [3–6]. Well documented risk factors include obesity, smoking, excessive alcohol intake, and chronic gastrointestinal reflux disease (GORD). Centripetal obesity and chronic GORD are particularly associated with adenocarcinoma

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and have contributed to its continued increase in incidence over recent years. Eliminating obesity could significantly decrease oesophageal adenocarcinoma incidence (up to three fold), and educating patients of the clinical presentation of GORD and encouraging them to seek early medical attention and treatment may have an even greater benefit [3,6].

Dietary agents including vitamins C and E, selenium and carotenoids have been shown to possess antioxidant properties which can reduce DNA damage and up-regulate apoptosis thereby potentially minimising the risk of cancer [7,8]. Encouraging results have been obtained from animal studies where vitamin E supplementation has been shown to suppress the development of oesophageal adenocarcinoma [9]. However, these promising results are not universally reported [10] and further work is needed to correlate specific dietary supplements with cancer risk as well as to address dose–response and duration requirements.

3. Chemoprevention

Several well-established medications have demonstrated evidence of a chemoprotective effect and are currently undergoing substantial investigation. These include aspirin, non-steroidal anti-inflammatories, and proton pump inhibitors. In addition to these established drugs, there is considerable optimism that our improving understanding of carcinogenesis will allow development of highly targeted disease specific agents.

The only widely recommended medication for chemoprevention and/or symptom control in patients with Barrett's oesophagus is protein pump inhibitors (PPIs). Recurrent pulsatile acid reflux in the lower oesophagus has been shown to predispose to the development of Barrett's oesophagus, a potential precursor of oesophageal adenocarcinoma. By reducing the acidic component of oesophageal refluxate PPIs decrease cellular differentiation and down-regulate COX-2 expression. However, to date clinical trials of PPIs in Barrett's oesophagus have failed to demonstrate a significant reduction in adenocarcinoma rates even in animal models [11,12], although initial fears that PPIs could actually stimulate hyperproliferation of Barrett's epithelium by induction of hypergastrinaemia appear dumfounded [13–15].

Both aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) have been associated with a reduction in progression to oesophageal adenocarcinoma when taken regularly and for a sufficient duration [16,17]. The precise mechanisms for this are unclear but it is most likely mediated via inhibition of COX-2 with simultaneous inhibition of other inflammatory pathways. High dose aspirin has been shown to produce a 33% reduction in the odds of developing oesophageal adenocarcinoma, with evidence of a dose–response effect in reducing the odds of progression with increasing dosage [18]. Its primary current clinical indication is to decrease mortality from ischaemic heart disease, peripheral vascular disease and cerebrovascular disease albeit the lower dose of 75 mg per day is effective for these purposes. Prolonged aspirin usage, particularly at higher doses, confers a risk of serious gastrointestinal haemorrhage and could therefore not been recommended as a sole primary prevention agent [18].

The Aspirin Esomeprazole Chemoprevention Trial (AspECT) trial is a large ongoing phase 3 UK-based randomised trial which aims to assess the role of aspirin plus esomeprazole on the overall mortality of patients with Barrett's oesophagus [19]. It is hypothesised that the combined use of aspirin with esomeprazole could mitigate the risks of gastrointestinal haemorrhage whilst providing combined vascular and anti-cancer benefits. It is important to highlight that chemoprevention using aspirin does not appear effective in all patients with Barrett's oesophagus as up to 80% have been shown to derive no cancer prevention benefit [20]. In addition, if the AspECT trial is to recommend esomeprazole-aspirin therapy for patients with Barrett's oesophagus it will likely spawn further studies aiming to establish ways of determining the 20% of patients with Barrett's oesophagus who appear to derive benefit from aspirin therapy [20].

Statins and 5-aminosalicyclic acid (5-ASA) compounds are also widely reported to possess chemopreventive properties although the later have a considerable side–effect profile making their use solely for chemoprevention impractical [21]. A recent meta-analysis of 11 observational studies examining adenocarcinoma development in Barrett's oesophagus included 317 cancers and 1999 controls and demonstrated that routine statin use was associated with a significant reduction in the incidence of adenocarcinoma (OR = 0.57; 95% CI: 0.43–0.75). Pooled data from population-based studies also showed that statin use was associated with a lower incidence of all combined esophageal cancers (OR = 0.81; 95% CI: 0.75–0.88) in an unselected population cohort [22]. Large-scale trials with long-term follow-up are currently underway to further evaluate and quantify the potential benefits of statin use in the prevention of oesophageal and other gastrointestinal malignancies.

It is hoped that the development of molecular techniques will enable future biotherapeutic targeting of the molecular modulators essential for carcinogensis. Since many common cancers share similar origins with dysfunction in mismatch-repair mechanisms, oncogenes and angiogenic pathways it is feasible that novel agents could demonstrate widespread oncological chemopreventive benefits.

4. Intervention for oesophageal dysplasia

Barrett's oesophagus confers a 30–125 times increased risk of oesophageal adenocarcinoma and has a population prevalence of around 2% [23]. The reported risk of progression from Barrett's oesophagus to adenocarcinoma varies but is in the region of 0.3% per year [24]. However, the development of dysplastic Barrett's oesophagus confers a much higher risk of progression to adenocarcinoma. There is clear evidence for the early endoscopic treatment of high-grade dysplasia (HGD) which can prevent malignant progression and confer long-term survival benefits [25–29]. There is also very recent evidence from a multi-centre randomised trial to support the early endoscopic treatment of Barrett's-associated low-grade dysplasia (LGD) provided the diagnosis has been confirmed by two expert gastrointestinal histopathologists [30]. After 3 years of follow-up, RFA therapy was shown to decrease the risk of progression from LGD to adenocarcinoma by 7.4% compared to endoscopic surveillance alone (1.5% ablation group vs 8.8% control group; 95% CI 0%–14.7%; $p = 0.03$) [30].

Endoscopic mucosal resection (EMR) is recommended for excision and accurate staging of focal dysplastic lesions and has been shown to provide complete remission in 97% of patients with high-grade lesions smaller than 2 cm in diameter [31]. A consensus of international experts support the subsequent use of radiofrequency ablation (RFA) to the whole Barrett's segment once focal lesions have been excised [29]. This policy destroys the underlying field change associated with dysplastic Barrett's oesophagus and thereby minimises the risk of recurrence.

RFA has recently become the most favoured ablation technique and has demonstrated eradication of Barrett's oesophagus with or without dysplasia in up to 98% of patients at 21 months, with a very low incidence of complications [18,32,33]. This effect has also been shown to be durable at 3 years although longer term follow-up data is awaited.

Other ablation therapies including photodynamic therapy, argon plasma coagulation (APC), and multipolar electrocoagulation