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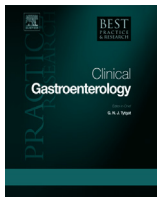

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Barrett's oesophagus: Can meaningful screening and surveillance guidelines be formulated based on new data and rejigging the old paradigm?

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A B S T R A C T

Gastro-oesophageal reflux disease (GORD) and Barrett's oesophagus (BO) have been considered to be the most important known risk factors for oesophageal adenocarcinoma (OAC). It has been the fastest growing cancer in the Western World and has occurred against a backdrop of progressive reduction in the risk estimate of malignancy associated with BO and no reduction in mortality from OAC using the prevailing screening and surveillance guidelines. The recently published link between high risk HPV and Barrett's dysplasia/cancer may be the 'missing' strong risk factor responsible for the significant rise of OAC since the 1970's, as has been the case with head and neck tumours, another viral associated cancer. P53 immunohistochemistry has been proposed as a good molecular marker for predicting disease progression in BD. Nevertheless, significant negative staining for this mutation in BD remains a major hurdle to widespread routine clinical use as a sole molecular marker. Recent data raises the distinct possibility of at least 2 (probably more) carcinogenic pathways operating in OAC. One is

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HPV mediated devoid largely of p53 mutations and the other p53 dependent. The joint use of both these markers as part of a molecular panel may represent the best bet yet of detecting the high risk group of progressors to OAC. Patients who are positive for either or both biomarkers i.e p53 or/and transcriptional markers of HPV may warrant more intensive screening. In future, genome wide technology may provide molecular signatures to aid diagnosis and risk stratification in BO.

Introduction

Gastro-oesophageal reflux disease (GORD) and Barrett's oesophagus (BO) are the most important known risk factors (as yet) for oesophageal adenocarcinoma (OAC). In a study by Lagergren, persons with chronic frequent and severe GORD symptoms had an odds ratio (OR) of 43.5 for OAC [1]. Currently, BO is the only recognized visible precursor lesion for OAC with a malignant potential currently estimated at between 0.12 and 0.13% per annum [2,3]. Previously, the cancer risk in BO had been estimated to be approximately 1.0% per year (one case per 125 patient-years) but there has been progressive downgrading over time to one case per 200 patient years and even one case per 300 patient-years [4,5]. Advanced OAC is a highly lethal cancer with a 5 year survival rate of less than 15% [6]. Nevertheless, those with early stage oesophageal malignancy (T1) (representing <10% of those undergoing oesophagectomy) have a more than 90% survival rate at 5 years [7].

OAC is one of the fastest growing cancers in the Western World [8], though recently, the rate of increase has diminished and possibly plateaued in the US and Sweden [9,10]. This 'epidemic' of OAC has occurred against a backdrop of progressive reduction in the risk estimate of malignancy associated with BO [11]. It has been suggested that to 'explain a rise of oesophageal adenocarcinoma of this magnitude, the prevalence of a strong risk factor must also rise exponentially-as was the case for smoking and lung cancer. Such a risk factor has not been identified and defining it should be a priority' [8]. The recent discovery of a strong association of transcriptionally active high-risk human papillomavirus (hr-HPV) with Barrett's dysplasia (BD) but not BO [12] may potentially be this strong risk factor responsible for the significant rise of OAC since the 1970's, as has been the case with head and neck tumours, another viral associated cancer [13–15]. It has been reported that the prevalence of HPV in oropharyngeal cancers increased from 16% in the 1980's to 73% in the 2000's accounting for an increase of incidence of 0.8 cases/100,000 subjects to 2.6/100,000 in that time frame [13]. It begs the question: has too much significance been attached to BO per se rather than other risk factors (both known and unknown) involved either in the progression along the metaplasia–dysplasia–adenocarcinoma sequence or independent of this multi-step pathway [11]? Evidence for other risk factors irrespective of BO/GORD is suggested by the fact that the vast majority of OAC patients had no prior diagnosis of BO and 40% of those with oesophageal malignancy reported no history of frequent heartburn [1,16] and that surveillance of patients with columnar lining/specialized intestinal metaplasia of the oesophagus has not been shown to reduce mortality from adenocarcinoma. Absence of a universal consensus on the definition of BO centred on the use of the word 'goblet cell' or otherwise is unhelpful as there is still a risk of malignant progression in patients without intestinal metaplasia (0.07% per year) as compared to those with intestinal metaplasia (0.38% per year) on index biopsy [2]. To further murky the waters, some (including the author) consider it an adaptive epithelium developed to withstand the harsh and corrosive elements of acid/pepsin/bile in the lower third of the oesophagus [17–19]. No wonder BO continues to be an enigma since it was first described more than 60 years ago!

BO is named after an Australian born British surgeon, Norman Barrett, who considered it as 'the lower oesophagus lined by columnar epithelium' [20] after revising his earlier definition (columnar lined congenitally short oesophagus due to the stomach being trapped in the chest) [20] based on the