

## Managing Barrett's oesophagus

### *Can chemoprevention reduce the risk of progression to malignancy?*

ONCE A RARE TUMOUR, adenocarcinoma of the oesophagus has tripled in incidence in Australia over the past 20 years (Ian McDermid, Australian Institute of Health and Welfare, personal communication). This increase, together with the dismal 5-year survival of patients with this cancer, has focused attention on its risk factors. The strongest of these are symptomatic gastro-oesophageal reflux disease and Barrett's oesophagus, a condition in which the squamous lining of the lower oesophagus is replaced by metaplastic columnar epithelium.

Based on postmortem studies, Barrett's oesophagus probably affects about 1% of the population in the United States and, at endoscopy, one in five to 10 patients with gastro-oesophageal reflux.<sup>1</sup> Evidence of Barrett's oesophagus (or at least intestinal metaplasia) is commonly found in resection specimens for oesophageal cancer.<sup>1</sup>

When Barrett's oesophagus is found at endoscopy, the appropriateness of the patient entering a surveillance program may be considered, with the aim of reducing the risk of death from oesophageal adenocarcinoma. These programs involve regular endoscopy with multiple biopsies from the metaplastic epithelium and interpretation by a skilled pathologist.

The rate at which malignancy develops in patients undergoing surveillance has been overestimated in the past because of publication bias; a reasonable estimate appears to be about 1 tumour in 200 patient-years of surveillance.<sup>2</sup> The absolute lifetime risk of an individual with Barrett's oesophagus developing oesophageal adenocarcinoma is probably about 1 in 20, which is comparable to the community risk for developing colorectal cancer. The average age for developing oesophageal adenocarcinoma is the mid to late 60s, but only a few patients with Barrett's oesophagus die of oesophageal cancer, as comorbidities are common.<sup>3</sup>

Given these facts, and the problem of ensuring compliance with surveillance, it is not surprising that it has been difficult to demonstrate that surveillance programs reduce mortality, either overall or from oesophageal cancer. The only positive evidence that surveillance improves outcomes derives from the results of surgery on patients with surveillance-detected tumours. These patients generally fare better than those who are diagnosed after presenting with symptoms. Although individual patients may benefit from surveillance, the overall community benefit and cost-effectiveness of these programs is still debated (particularly for programs not conducted in well organised centres by enthusiasts with access to specialist pathologists).<sup>4</sup> The use of biomarkers, such as aneuploidy or molecular markers, may help predict the risk of malignancy and may be useful in targeting surveillance programs.<sup>5</sup>

If surveillance of patients with Barrett's oesophagus is unrewarding, are there ways to retard the neoplastic process? Recently, the pathobiology of Barrett's oesophagus has come under intense scrutiny, and it is likely that repeated exposure of the lower oesophagus to reflux of acid and bile is

a major factor resulting in metaplasia and subsequent dysplasia.<sup>6</sup> Molecular changes in the pathway to malignancy have been identified, including upregulation of cyclo-oxygenase-2 (COX-2).<sup>7</sup>

The study reported by Hillman and colleagues in this issue of the Journal (*page 387*) examines the effect of acid suppression on the development of dysplasia in Barrett's oesophagus.<sup>8</sup> The authors analysed the pathology findings from a group of patients enrolled in a surveillance program over the period of time during which proton-pump inhibitors (PPIs) were introduced. The rates of development of dysplasia and malignancy were examined before and after patients started taking PPIs. Although the results must be interpreted in the light of the lack of randomisation, the time effects, and difficulties in distinguishing low-grade dysplasia from inflammatory atypia (problems which the authors recognised and corrected for as far as possible), the study does demonstrate an effect of acid suppression on the development of dysplasia and malignancy. Over 50% of patients (a somewhat high figure) developed low-grade dysplasia within 3 years while not taking PPIs, but this percentage was reduced by almost two-thirds in patients taking PPIs. Interestingly, the dysplasia-free survival curves diverged after only months, suggesting that the effect was rapid.

If acid suppression were efficacious in reducing the risk of malignancy, it would be an attractive chemopreventive option, as:

- it is the cornerstone of therapy for gastro-oesophageal reflux disease, with which Barrett's oesophagus is closely associated;
- powerful acid-suppressant drugs are available; and
- a reduction in gastric acid exposure leads to a concomitant reduction in bile exposure.

Combining acid suppression with COX inhibitors (especially aspirin) has further attractions, as COX inhibition alone may reduce the incidence of oesophageal carcinoma by up to half,<sup>9</sup> and some of its risks would be ameliorated by acid suppression. COX inhibitors may have an additional benefit on cardiovascular risk in this group of patients. Studies to investigate these issues are under way.

So how will this information help us control oesophageal adenocarcinoma? In particular, if acid suppression does reduce the rate of progression of Barrett's oesophagus to low-grade dysplasia, will this translate into a reduction in the incidence of oesophageal adenocarcinoma? The natural history of low-grade dysplasia is not well defined, while even that of high-grade dysplasia has been debated,<sup>10</sup> with the estimated cumulative incidence of cancer varying dramatically between studies, from 56% at 3 years to only 9% at 5 years. The most efficacious method of preventing gastro-oesophageal reflux is good antireflux surgery, so, if control of acid and bile reflux alone were the answer, one might expect to see a dramatic reduction in the rate of oesophageal adenocarcinoma after fundoplication. Unfortunately, this

has not been the case.<sup>11</sup> One might also predict that the increasing use of proton-pump inhibitors in the past decade, and particularly in the past few years, would reduce the rate of oesophageal adenocarcinoma. However, this effect is not yet evident either in follow-up of patients prescribed omeprazole,<sup>12</sup> or in national cancer monitoring (Ian McDermid, Australian Institute of Health and Welfare, personal communication).

Even if chemoprevention using potent acid suppression, with or without COX inhibition, can be shown to slow development of malignancy, given the modest absolute risks (1 per 20 patients with Barrett's oesophagus and perhaps 1 per 200 of those with gastro-oesophageal reflux), we must still identify and target appropriate groups for this or other interventions. We must also carefully examine strategies for efficacy and cost effectiveness. Low-risk strategies, such as chemoprevention, may be broadly applicable, whereas intensive strategies, such as endoscopic surveillance with examination of biopsy specimens for biomarkers of malignancy, will need to be targeted to high-risk groups.<sup>13</sup>

The jury is still out.

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**Competing interests:** GSH has acted as a consultant to AstraZeneca, Novartis and Pharmacia (Pfizer), and has received research support, sponsored travel and honoraria for speaking from AstraZeneca, Novartis and Wyeth. SN has acted in an advisory capacity to Pharmacia and has received research support, sponsored travel and honoraria for speaking from AstraZeneca and Pharmacia (Pfizer).

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