Acid inhibitory medication and risk of gastric and oesophageal cancer

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What are the long term effects of acid suppressive medication on the risk of gastric and oesophageal cancer?

It is now 30 years since effective antisecretory drugs in the form of H_2 receptor antagonists became available for use in clinical practice. Since then the use of medications which elevate intragastric pH has progressively increased and a significant proportion of the population is taking powerful antisecretory medication on a long term basis. In view of the recognised association between hypochlorhydria and gastric cancer,^{1,2} there has been concern that long term use of acid suppressive medication might increase the risk of this sinister condition. In this issue of *Gut*, García Rodríguez and colleagues³ report the association between long term antisecretory medication and upper gastrointestinal cancer (see page 1538).

The study used the UK general practitioners research database (GPRD) which is a primary care automated database initiated in the late 1980s and currently including more than 3 million subjects. It contains detailed information on patient demographics, diagnosis, and drug prescriptions. The information is automatically transferred from the general practitioner's computer to the database. The current study was based on a cohort of all individuals registered on the GPRD aged 40–84 years during the period January 1994 to December 2001. Over the 4 340 207 person years of follow up, 287 oesophageal adenocarcinoma, 195 gastric cardia adenocarcinoma, and 327 gastric non-cardia adenocarcinoma were diagnosed. Patients who developed upper gastrointestinal cancers during the study period were compared with 10 000 matched controls from the database.

Adenocarcinoma of the oesophagus and stomach occurred more frequently in those taking antisecretory medication compared with controls who had never received such medication. Patients taking acid suppressing drugs for more than three years had a threefold increased risk of oesophageal adenocarcinoma (odds ratio (OR) 2.99 (95% confidence interval (CI) 1.95–4.59)) and a twofold increased risk of gastric non-cardia adenocarcinoma (OR 2.00

(95% CI 1.24–3.20)) compared with non-users. The association between the use of this medication and gastric and oesophageal adenocarcinoma remained significant after correction for age, sex, calendar year, smoking, alcohol consumption, and body mass index. No associations were found between long term acid suppressing drugs and the risk of gastric cardia adenocarcinoma. The authors proceeded to investigate the possible mechanisms of the association between acid suppressive drug usage and increased risk of gastric and oesophageal adenocarcinoma.

They firstly assessed whether the association might be explained by an effect of the disease for which the drug was being prescribed rather than an effect of the medication itself. Gastro-oesophageal reflux is an important risk factor for oesophageal adenocarcinoma^{4–8} and also a major indication for prescribing acid inhibitory agents. The long term use of acid suppressive drugs for oesophageal indications had a greater than fivefold increased risk of oesophageal adenocarcinoma (OR 5.42 (95% CI, 3.13–9.39)) whereas there was no statistically significant increased risk of oesophageal adenocarcinoma when the drugs were prescribed for other indications. This is consistent with the increased risk of oesophageal adenocarcinoma in patients receiving acid suppressive medication, being an effect of the underlying reflux disease for which the drugs are being prescribed.

The fivefold increased risk of oesophageal adenocarcinoma in patients with reflux symptoms receiving long term acid suppressive therapy also indicates that such treatment does not remove the risk of malignant complications of the disease. This is consistent with other studies.^{4–6} Acid suppressive therapy is highly effective in treating erosive oesophagitis and its symptoms but to date there is no evidence that the treatment reduces the risk of oesophageal adenocarcinoma. The development of adenocarcinoma of the oesophagus is thought to be a multistage process with

erosive oesophagitis progressing to metaplasia and then dysplasia and then cancer.⁹ One cannot assume that treatments which are beneficial for erosive oesophagitis will necessarily be beneficial in the later steps of the pathway. The ASPECT trial is examining the effects of proton pump inhibitor therapy on the risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus although lack of a placebo limb may undermine the conclusion.

The study also showed that antisecretory medication was associated with an increased risk of non-cardia gastric cancer and it is much more difficult to determine whether this is an effect of the drug or of the disease for which the drug was prescribed. The problem in this case is that there is no common indication for acid suppressive therapy which has been shown to be definitely associated with an increased risk of non-cardia gastric cancer. The authors did observe that patients who received antisecretory medication for peptic ulcer indications had an increased risk of non-cardia gastric adenocarcinoma but there was no significantly increased risk in those who received the medication for other indications consisting mainly of reflux disease. One difference between these two groups would be their *Helicobacter pylori* status, with the ulcer group being largely positive and the reflux patients being largely negative.^{10,11} The difference in the risk of non-cardia adenocarcinoma might therefore be due to the known association of this cancer with *H. pylori* infection.¹² However, it is also possible that the acid suppressive therapy is increasing the risk of the cancer in the subgroup with *H. pylori* infection. Proton pump inhibitor therapy changes the pattern of gastritis in duodenal ulcer patients from an antral predominant gastritis to a body predominant gastritis¹³ which is the pattern associated with an increased risk of non-cardia gastric cancer.¹⁴ It is impossible to determine whether the increased risk of non-cardia cancer in patients receiving acid suppressive therapy for peptic ulcer indications was an effect of the original disease or an effect of the drug on that disease process. It will be interesting to see whether the increased risk of non-cardia gastric cancer in patients receiving acid suppressive therapy for peptic ulcer indications changes with the widespread eradication of *H. pylori* infection in ulcer patients and widespread eradication of the infection prior to long term acid suppressive therapy.

Strengths of this study include its size, general population base, prospective nature, and comprehensive documentation of patient information. These

strengths are all due to the development of the GPDB allowing automated collection of information which is then available for addressing important questions. It is to be hoped that the increasing privacy of information legislation does not restrict and complicate future use of this key database.

The major weakness in this study investigating the association between acid suppressive therapy and the risk of gastro-oesophageal cancer is the relatively short duration of acid suppressive therapy. The longest exposure to the medication was three years and the majority were taking it for less than one year. This cannot be considered to be long term in the time scale of cancer development. *H. pylori* infection is usually acquired in the first few years of life but the cancer which it gives rise to does not usually manifest itself until 50–70 years later. Exposure to anti-secretory medication for at least 10 times the length of exposure examined in the current study would be required before one could make any confident conclusions regarding either adverse or beneficial effects of such treatment on

cancer risk. Hopefully, the authors will be able to use the established database to subsequently examine true long term effects of acid suppressive medication on the risk of gastric and oesophageal cancer.

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Pancreatic cancer

An unfavourable prognosis for pancreatic cancer indicates fields of opportunity

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Large fields of cancerisation may give more aggressive, but easier to detect, pancreatic ductal adenocarcinoma

Prognosis for patients with pancreatic ductal adenocarcinoma (pancreatic cancer) is notoriously bad. In a study published in this issue of *Gut*, Kim and colleagues¹ make it clear that K-ras mutation in apparently benign pancreatic tissue at some distance from the tumour contributes to poor survival (see page 1598). This could indicate the presence of occult tumour cells in the resection margin but could also indicate that tumours developing in a large field of mutation carrying cells are more aggressive. This offers hope to patients where resection leaves behind no mutant cells in the margin but also suggests that the most aggressive tumours might prove to be the easiest to detect in asymptomatic patients.

A cynical reader might be forgiven for passing over the article by Kim and colleagues.¹ The paper talks of an unfavourable prognosis for patients with pancreatic cancer—cynics will respond with the observation that prognosis for pancreatic cancer is death, how much more unfavourable can it be? The paper also talks about K-ras gene mutations—cynics may groan and remember the many reports on K-ras mutations going back to the 1980s. Some may even remember a happier time when they believed that these mutations might serve as a marker for cancer, a time before it became apparent that such mutations are common in people with benign conditions. Some readers will be tempted to read on when

they notice that the abstract refers to K-ras mutations in resection margins histologically free of invasive cancer; these readers will be rewarded with an optimistic report that may prove of immediate clinical value and furthermore gives some exciting new insights into the different ways in which pancreatic cancer could develop.

Kim and colleagues¹ describe a cohort of 70 pancreatic cancer patients who underwent pancreatic resection of whom 31 were still alive after five years of follow up. Ten year survival (effectively cure) was approximately 20%. This seems extraordinary when compared with the often quoted statistic that the mortality of pancreatic cancer is equivalent to its incidence. The apparent ability of this group to cure what is often described as an incurable disease is also not explicable by misdiagnosis of patients as specimens from the longest survivors underwent independent pathological re-review confirming pancreatic ductal adenocarcinoma. The explanation could be the high quality of care received by patients at the John Wayne Cancer Institute and the UCLA School of Medicine, but although this undoubtedly contributed to survival, many other centres offer equally high standards and the truth is that these values are actually not inconsistent with a number of other recent reports (as the authors point out). In this respect,