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Cancer of the gastric cardia

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Current evidence indicates that cardia cancers are of at least two distinct and disparate aetiologies. One type resembles cancer of the more distal stomach (Type A), being a consequence of atrophic gastritis due to *Helicobacter pylori* infection or more rarely autoimmune atrophic gastritis. Another type (Type B) resembles oesophageal adenocarcinoma and is likely to be a consequence of short-segment gastro-oesophageal reflux disease. The two cancers are themselves indistinguishable but examination of the gastric phenotype indicates the aetiology: Type A occurring in patients with evidence of atrophic gastritis whereas Type B occurs in subjects with healthy acid secreting stomachs. In subjects with healthy acid secreting stomachs the cardia has a specific luminal chemistry remaining highly acidic and unbuffered following a meal and having very active nitrosative chemistry due to the acidification of nitrite in saliva. This luminal chemistry may contribute to the high incidence of metaplasia and neoplasia at this anatomical site.

Key words: gastric cancer; cardia; *H. pylori*, carditis; atrophy.

Until recently, the major way in which gastric cancer was sub-classified was according to its Lauren histological subtype, i.e. whether it was intestinal, diffuse or of undetermined histological subtype.[1] It was recognised that the epidemiology and aetiology of these histological subtypes of cancers were different. For example, the intestinal type of cancer increased exponentially with age, was more common in males than females and developed against the background of atrophic gastritis usually due to *H. pylori* infection. In contrast,[1–3] the diffuse type of cancer was more common in females, did not increase exponentially with age, sometimes developed in the absence of atrophic gastritis or even *Helicobacter pylori* and often had a strong familial tendency.[1–3]

Recently, evidence has emerged that gastric cancer should also be sub-classified according to whether it arises in the proximal cardia region of the stomach versus the more distal stomach. This is based upon evidence that cancers at these two anatomical sites differ with respect to both their epidemiology and pathogenesis. Gastric cancer is

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therefore now sub-classified according to both its histological subtype and according to whether it is located in the cardia or non-cardia region of the stomach.

WHAT IS THE GASTRIC CARDIA?

Before discussing cancer of the gastric cardia, it is necessary to define what is meant by the gastric cardia and cardia mucosa. Indeed, the aetiology of cardia cancer is probably closely related to the origins of cardia mucosa. The cardia is the most proximal part of the stomach adjoining the oesophagus. The mucosa of the cardia is similar to that of the antrum being columnar in type with branched mucus secreting glands and absent or very sparse acid secreting parietal cells and pepsin-secreting chief cells. The mucosa of the cardia abuts proximally with the squamous mucosa of the distal oesophagus and distally with the oxyntic mucosa of the body of the stomach. There may be a transition zone between the cardia and oxyntic cardia mucosa with a low density of parietal and chief cells referred to as cardia-oxyntic mucosa.

ENLARGEMENT OF THE CARDIA MUCOSA BY PROXIMAL AND DISTAL EXTENSION

There has been considerable debate recently as to whether cardia mucosa is present in the stomach in its pristine state or is entirely acquired as a result of columnar metaplasia of the distal squamous oesophagus. Chandrasoma et al examined the histology of the GE junction in autopsy samples.[4] Cardia and oxyntic cardia mucosa were present only in part of the circumference of the junction in 50% of specimens. The length of cardia plus oxyntic mucosa was less than 5 mm in 76% of patients. There was a tendency for the presence and extent of cardia mucosa to increase with age. They concluded that cardia mucosa was most probably an acquired structure due to gastro-oesophageal reflux. In order to further investigate this, De Hertagh et al performed detailed studies of the histology of the gastro-oesophageal junction in neonates.[5] They found that there was a very short segment of cardia-type mucosa (0.3–0.6 mm) in length and concluded that it was a normal structure, albeit very small in size. Consistent with this, studies in adults have found that a biopsy taken at the gastro-oesophageal junction and only a millimetre or two in length may contain oesophageal squamous mucosa, gastric cardia mucosa and gastric oxyntic mucosa.[6]

However, there is also evidence that cardia-type mucosa may be acquired and probably acquired by two different mechanisms. The first of these mechanisms is by columnar metaplasia of the distal squamous oesophageal mucosa so that it resembles cardia mucosa.[6–9] This causes proximal extension and enlargement of the apparent cardia mucosa of the stomach. Columnar metaplasia of the oesophagus is thought to occur due to frequent refluxing of acidic and proteolytic gastric juice onto the squamous mucosa of the distal oesophageal mucosa. The squamous mucosa of the oesophagus, unlike the columnar mucosa of the stomach, is not designed to withstand exposure to gastric juice and it develops superficial erosions and ulceration. This recurrent damage to the oesophageal mucosa causes it to undergo metaplasia and transform from squamous-type mucosa to a columnar mucosa which may be indistinguishable from cardia mucosa. This metaplastic columnar mucosa may also have focal regions of intestinal metaplasia within it.[6–10] However, this does not help distinguish it from the original cardia mucosa which also may have intestinal metaplasia within it due to the effects of *H. pylori* infection. In some subjects, the columnar metaplasia of the oesophagus