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European Journal of Cancer 39 (2003) 2487–2494

European Journal of Cancer

www.ejconline.com

Are carcinomas of the cardia oesophageal or gastric adenocarcinomas?

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Received 14 April 2003; received in revised form 23 June 2003; accepted 25 July 2003

Abstract

There is a clear relationship between Barrett's oesophagus and oesophageal adenocarcinoma, and between *Helicobacter pylori* and gastric cancer, but the histogenesis of cardiac adenocarcinomas is unknown. Some clues as to possible disease associations may be provided by the pattern of gastritis. In our study, we analysed gastritis associated with oesophageal, cardiac and gastric adenocarcinomas according to the Sydney classification. Chronic gastritis was more common in gastric (88%) than in cardiac (56%) and oesophageal adenocarcinomas (38%). *H. pylori* was significantly more prevalent in gastric (73%) than in cardiac (34%) or oesophageal (21%) adenocarcinomas. Our results show that factors other than *H. pylori* must be involved in the histogenesis of cardiac adenocarcinomas. As the pattern of gastritis and the clinical features of cardiac adenocarcinomas are more comparable to oesophageal carcinomas than gastric carcinomas, we speculate that most of these tumours share similar aetiological factors with oesophageal carcinomas.

Keywords: Gastritis; *Helicobacter pylori*; Barrett's oesophagus; Gastro-oesophageal reflux; Gastric cancer; Cardiac cancer; Oesophageal cancer

1. Introduction

Epidemiological studies reveal that gastric cancer is the second most common cause of cancer mortality worldwide [1]. However, during the past few decades the overall incidence rates of gastric adenocarcinomas have gradually decreased in the United States of America (USA) and Western Europe, but this decline does not apply to all forms of gastric cancer [2,3]. In contrast to the decline in the incidence of gastric cancer, the incidence rates of cardiac cancer have dramatically increased, up to 4–5% annually in the USA [4]. Simultaneously, there has been a dramatic shift in the incidence of oesophageal squamous carcinomas towards adenocarcinomas, as a result of which the latter account for 50% of the oesophageal cancers in Western Europe and USA [5]. In keeping with the parallel increase in incidence, oesophageal adenocarcinomas and cardiac adenocarcinomas share some epidemiological features, which distinguish them from adenocarcinomas of the distal part of the stomach. There is an equal gender distribution in gastric carcinomas, but the male/female ratio in oesophageal and cardiac carcinomas is 9.2 and 5.5, respectively. The disease, both in the distal oesophagus and the cardia, is most common in middle-aged patients [6]. A survival analysis has shown that patients with an adenocarcinoma of the cardia have a similar survival to those having an adenocarcinoma of the distal oesophagus [7].

The dramatic increase in incidence of oesophageal carcinomas is related to the well-established association

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doi:10.1016/S0959-8049(03)00664-6

of gastro-oesophageal reflux and Barrett's oesophagus [8]. Additional risk factors, involved in the development of oesophageal adenocarcinomas, are smoking and a poor socio-economic status. According to some authors, these risk factors are also found in association with cardiac adenocarcinomas [9,10]. Other studies could not confirm these results and showed either no relationship or an opposite relationship in which a high socio-economic status was related to cardiac cancer [11,12]. Some authors found that smoking was associated with a higher risk for the development of gastric cancer [13,14]. Thus, neither smoking nor socio-economic status could allow differentiation of risk by anatomical sub-site.

In contrast to the plethora of studies concerning the aetiopathogenesis of oesophageal adenocarcinoma, the histogenesis of cardiac adenocarcinomas is less clear. Although both adenocarcinomas share similar epidemiological characteristics, the relationship between gastro-oesophageal reflux and adenocarcinomas of the cardia is less obvious. According to some authors, 'carditis' is a more sensitive marker of gastro-oesophageal reflux that could even precede the clinical signs of refluxoesophagitis. Others, however, could not confirm this [15–17]. They believe that inflammation of the cardia is part of a *Helicobacter pylori*-related pangastritis. However, the role of *H. pylori* in the development of cardiac adenocarcinomas is uncertain. For example, the rising incidence of cardiac cancers is in contrast to the decline of *H. pylori* infection in the same populations. The relationship between *H. pylori* chronic pangastritis and gastric cancer is more firmly established, as the infection is associated with a 9-fold increased risk for this type of cancer [18]. As would be expected, the decrease in *H. pylori* infection is paralleled by a decline in the prevalence of gastric cancer [19].

Hence, the purpose of this study was to analyse the inflammatory changes present in the gastric mucosa in cases of oesophageal and cardiac adenocarcinomas, according to the updated Sydney system [20]. The same assessment has been performed on gastric biopsies of a control population with gastric carcinomas. Special attention has been given to the presence of *H. pylori* in the inflamed mucosa.

2. Patients and methods

Our retrospective study comprised 342 patients, who underwent surgery for an adenocarcinoma of the oesophagus or stomach between 1993 and 2000 at the University Hospitals in Leuven, Belgium. The tumours were classified as oesophageal, cardiac or gastric cancer on the basis of two parameters: (1) the localisation of the major bulk of the tumour, and/or (2) the presence or absence of Barrett's oesophagus, determined on preoperative endoscopic biopsies or using tissue from the resection specimen, taken above the gastro-oesophageal junction.

A Barrett's oesophagus was defined as the replacement of squamous epithelium by an intestinal type of columnar epithelium, independent of the length of the lesion [21]. An alcian blue/periodic acid-Schiff (PAS) stain (pH 2.5) was done in order to detect goblet cells in the epithelium of a Barrett's oesophagus. This stain allows the distinction between neutral gastric (red) and acidic intestinal type (blue) mucins.

According to the advices of the International Union Against Cancer (UICC), cardiac tumours are defined as tumours of which the major part, i.e. more than 50%, is situated in the cardia, whereas in oesophageal adenocarcinomas more than 50% of the tumoral mass is located in the oesophagus. If the tumour is centred on the gastro-oesophageal junction, the UICC advise the tumour to be classified as being of oesophageal origin when there is co-existent Barrett's oesophagus, whereas in its absence the tumour is likely to be of cardiac origin [22].

Routine histology was performed on formalin-fixed and paraffin-embedded material. The adenocarcinomas and gastritis were evaluated on haematoxylin–eosin (H&E)-stained sections. The tumours were categorised into intestinal and diffuse type adenocarcinomas according to the Lauren classification. If tumours showed mixed histological characteristics, the predominant features determined which group of adenocarcinomas they belonged to [23]. Gastric cancers are either situated in the corpus and/or the antrum of the stomach. According to the classification of Mulligan, pylorocardiac gland carcinomas may have a papillary growth pattern, composed of cells having a clear cytoplasm. This histological subtype has not been described in oesophageal adenocarcinomas. Bulky tumours, of which the exact localisation at the gastro-oesophageal junction could not be determined, but showing these morphological features, were determined as being of cardiac origin [24].

Gastritis was analysed according to the updated Sydney classification and assessed on tissue blocks taken from the resection specimen at a distance from the tumour in order to avoid interference with the stromal inflammation in the neighbourhood of the tumour [20]. As most of our patients underwent a partial oesophagogastrectomy, the number of antral specimens was too low for analysis. Hence, the gastric inflammation in association with the different types of tumours has only been evaluated on corpus tissue. The different parameters scored included chronic inflammation (mononuclear inflammatory cells, e.g. lymphocytes, plasma cells), activity (polynuclear inflammatory cells), atrophy, intestinal metaplasia and *H. pylori* colonisation.

These parameters were graded from absent, mild, moderate to severe. A cresylviolet staining was performed in order to detect *H. pylori* infection.

Statistical analysis of the results was performed using the Chi^2 test, in which $p \leqslant 0.05$ was considered as statistically significant.

3. Results

3.1. Classification of the proximal tumours (Table 1)

The 342 tumours in our study population were classified according to the different criteria.

When we categorised our 242 proximal tumours according to the localisation of the bulk of the tumoral mass, 98 (40%) and 94 (39%) tumours were lower oesophageal and cardiac adenocarcinomas, respectively. 50 patients had a tumour centred on the gastro-oesophageal junction, and these tumours were classified as gastro-oesophageal junction-adenocarcinomas (21%).

A Barrett's oesophagus, as defined above, was diagnosed in 45% of patients ($n = 147/328$). The presence of a Barrett's oesophagus could not be evaluated in 18 patients, having a gastric cancer, as they underwent a partial gastrectomy. 20 of these patients with a Barrett's oesophagus had a gastric cancer (24%, $n = 20/82$). Purely based on the presence or absence of a Barrett's oesophagus (independently of other criteria), 127 (52%) and 115 (48%) proximal tumours may be classified as oesophageal and cardiac adenocarcinomas, respectively. However, in 10% of these adenocarcinomas with Barrett's ($n = 13/127$), the bulk of the tumour was situated in the cardia, whereas in 7% of the adenocarcinomas without Barrett's ($n = 8/115$) the tumour was predominantly located in the oesophagus.

According to the advice of the UICC, the proximal lesions were classified by combining the location of the bulk of the tumoral mass and the presence or absence of a Barrett's mucosa in 135 oesophageal adenocarcinomas (56%) and 107 cardiac adenocarcinomas (44%). The results will be described according to the latter classification unless otherwise specified.

3.2. Clinical data

The total study population ($n = 342$) had a mean age of 65 years (± 11 years) and was composed of 242 males and 100 females. Table 2 presents the clinical characteristics of all the patients included in this study. The age distribution was similar in the group of oesophageal and cardiac adenocarcinomas, whereas the group of gastric cancers were slightly older. Males and females were equally distributed in the latter group, but the group of oesophageal ($P = 0.00001$) and cardiac adenocarcinomas ($P = 0.001$) was predominantly composed of males.

3.3. Pathological features of the tumours

Our study population consisted of 135 oesophageal adenocarcinomas, which in 94% ($n = 127$) were associated with an intestinal type of Barrett's oesophagus. The length of the Barrett's oesophagus was on average 5 cm (± 3 cm). In 26% of these cases, the length of the Barrett's oesophagus was less than 3 cm. Unfortunately, the length of the Barrett's oesophagus could not be

Table 1
Classification of our study population ($n = 342$ adenocarcinomas)

Criterion	Proximal cancer			Distal cancer
	Oesophageal cancer	Cardiac cancer	GE junction cancer	Gastric cancer
Mass of tumour	98 (40%)	94 (39%)	50 (21%)	100 (100%)
Barrett's oesophagus	Present	Absent	NA	Present
	127 (52%)	115 (48%)		20 (24%)
UICC	135 (56%)	107 (44%)	NA	NA

NA, not applicable; UICC, International Union Against Cancer; GE, gastro-oesophageal.

Table 2
Clinical data for the patients

	Oesophageal cancer	Cardiac cancer	Gastric cancer	*P* value
Number of cases	135	107	100	
Mean age (range) (years)	63 (32–86)	64 (20–85)	68 (30–93)	
M/F ratio	5.75	4.1	1.4	0.00001,[a] 0.001[b]
Size of tumour (range) (cm)	4.88 (1–11)	5.78 (1–13)	5.1 (1–16)	

M, male; F, female.

[a] Oesophageal adenocarcinomas versus gastric adenocarcinomas.

[b] Cardiac adenocarcinomas versus gastric adenocarcinomas.

determined in all the cases as the presence of a bulky tumour (4.88 ± standard deviation (S.D.) of 2.26 cm, range 1–11 cm) hampered the detection of Barrett's oesophagus during gross examination. Most oesophageal adenocarcinomas were of the intestinal type (89%, $n = 120$), whereas 11% belonged to the diffuse type of adenocarcinomas ($n = 15$).

In accordance with the definition of the UICC, 107 tumours were categorised as cardiac cancers. Similar to the oesophageal adenocarcinomas, the tumours of cardiac origin were large tumours with an average diameter of 5.78 cm (S.D. of 2.43 cm, range 1–13 cm). In accordance with the Lauren classification, the prevalence of intestinal and diffuse type adenocarcinomas was 77% ($n = 82$) and 23% ($n = 25$), respectively.

In our group of gastric cancers, the tumour was more frequently situated in the antrum (48%) than the corpus (27%). In 25%, the tumour extended across both the antrum and corpus as a result of which the primary location of the tumour could not be determined. The prevalence of intestinal and diffuse type adenocarcinomas was nearly the same, namely 58 and 42%, respectively.

An adenocarcinoma of the pylorocardiac type, as described in Mulligan's classification, was found in 26 of the 342 cases (8%). 8 of these were gastric adenocarcinomas and the remainder were in the cardia group. Thus, 18 of 107 cardiac adenocarcinomas (17%) corresponded to the pylorocardiac gland type.

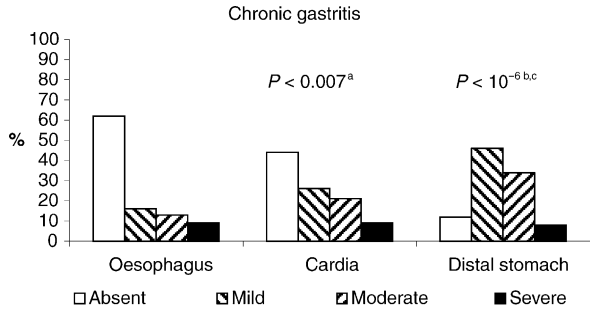

Fig. 1. Distribution of chronic gastritis in non-involved tissue in relation to the three sites of carcinoma. [a]Oesophageal adenocarcinomas versus cardiac adenocarcinomas; [b]oesophageal adenocarcinomas versus gastric adenocarcinomas; [c]cardiac adenocarcinomas versus gastric adenocarcinomas.

3.4. Grading of gastritis in association with the different types of cancer

In the oesophageal and cardiac adenocarcinomas, the prevalence of associated chronic gastritis differed significantly between the groups ($P < 0.007$), 38% ($n = 51/135$) and 56% ($n = 60/107$), respectively (Fig. 1, Tables 3 and 4). However, in gastric adenocarcinomas the gastric mucosa was nearly always infiltrated by mononuclear cells (88%), resulting in a significant difference in prevalence when compared with both oesophageal ($P < 10^{-6}$) and cardiac adenocarcinomas ($P < 10^{-6}$). In oesophageal cancers, most intestinal (60%, $n = 72/120$) or diffuse type adenocarcinomas (80%, $n = 12/15$) were associated with a normal gastric mucosa. However, normal mucosa was only observed in 33% of the intestinal type of cardiac adenocarcinomas ($n = 27/82$) ($P < 0.0004$). Nevertheless, no significant difference was observed between the diffuse type adenocarcinomas of the oesophagus (80%, $n = 12/15$) and those of cardiac origin (76%, $n = 19/25$). In contrast to these adenocarcinomas, both diffuse and intestinal type adenocarcinomas, situated in the stomach proper, were mostly associated with chronic gastritis. However, chronic gastritis was more frequently absent in the neighbourhood of diffuse type adenocarcinomas than in intestinal type adenocarcinomas.

Infiltration of the *lamina propria* with neutrophils was more common in association with gastric carcinomas (50%) than in oesophageal (18%) ($P < 10^{-6}$) and cardiac adenocarcinomas (26%) ($P < 0.0007$) (Table 3). The prevalence of atrophy in oesophageal, cardiac and gastric adenocarcinomas was 2% ($n = 3/135$), 7% ($n = 8/107$) and 26% ($n = 26/100$), respectively (Table 3). In 42% of the gastric adenocarcinomas, part of the epithelium

Table 3
Different parameters of gastritis in relationship to the different localisation of adenocarcinoma

	Oesophageal adenocarcinoma ($n = 135$)	Cardiac adenocarcinoma ($n = 107$)	Gastric adenocarcinoma ($n = 100$)	P value
Chronic inflammation	51 (38%)	60 (56%)	88 (88%)	< 0.007,[a] $< 10^{-6}$[b,c]
Activity	24 (18%)	28 (26%)	50 (50%)	$< 10^{-6}$,[b] < 0.0007[c]
Atrophy	3 (2%)	8 (7%)	26 (26%)	
Intestinal metaplasia	3 (2%)	11 (10%)	42 (42%)	$< 10^{-6}$[b,c]
Helicobacter pylori	29 (21%)	36 (34%)	73 (73%)	< 0.05,[a] $< 10^{-6}$[b,c]

[a] Oesophageal adenocarcinomas versus cardiac adenocarcinomas.
[b] Oesophageal adenocarcinomas versus gastric adenocarcinomas.
[c] Cardiac adenocarcinomas versus gastric adenocarcinomas.

Table 4
Different parameters of gastritis in relationship to intestinal and diffuse types of adenocarcinoma

	Oesophageal adenocarcinoma		Cardiac adenocarcinoma		Gastric adenocarcinoma	
	Intestinal ($n=120$)	Diffuse ($n=15$)	Intestinal ($n=82$)	Diffuse ($n=25$)	Intestinal ($n=58$)	Diffuse ($n=42$)
Chronic inflammation	48 (40%)	3 (20%)	54 (66%)	6 (24%)	56 (97%)	32 (76%)
Activity	22 (18%)	2 (13%)	25 (30%)	3 (12%)	26 (45%)	14 (33%)
Atrophy	2 (2%)	1 (7%)	8 (10%)	0 (0%)	19 (33%)	7 (17%)
Intestinal metaplasia	3 (2.5%)	0 (0%)	11 (13%)	0 (0%)	28 (48%)	14 (33%)
Helicobacter pylori	27 (22.5%)	2 (13%)	32 (39%)	4 (16%)	47 (81%)	26 (62%)

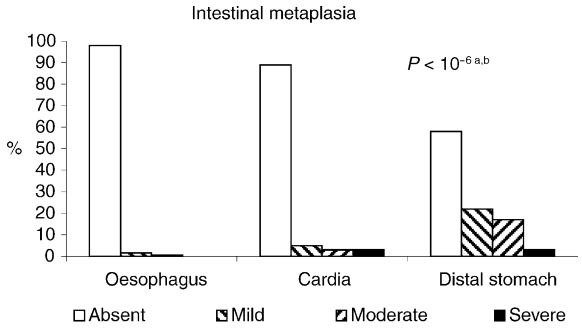

Fig. 2. Distribution of intestinal metaplasia in non-involved tissue in relation to the three sites of carcinoma. [a]Oesophageal adenocarcinomas versus gastric adenocarcinomas; [b]cardiac adenocarcinomas versus gastric adenocarcinomas.

showed intestinal metaplasia, which was more prevalent than in oesophageal (2%, $n=3/133$) ($P<10^{-6}$) and cardiac adenocarcinomas (10%, $n=11/107$) ($P<10^{-6}$) (Table 3). Intestinal metaplasia was mostly mild in oesophageal or cardiac adenocarcinomas, but 20% of the gastric adenocarcinomas had a moderate or severe degree of intestinal metaplasia (Fig. 2).

The overall prevalence of *H. pylori* was 40% ($n=138/342$), with a prevalence of 21% ($n=29/135$), 34% ($n=36/107$) and 73% ($n=73/100$) in oesophageal, cardiac and gastric carcinomas, respectively. Although the prevalence of infection in cardiac adenocarcinomas was significantly lower than in gastric adenocarcinomas ($P<10^{-6}$), there was also a significant difference when compared with oesophageal adenocarcinomas ($P<0.05$).

4. Discussion

It is commonly accepted that *H. pylori* is a risk factor for the development of gastric cancer. The histogenesis of this type of cancer is a multifactorial process involving a progressive evolution from superficial gastritis, atrophy, intestinal metaplasia, dysplasia to cancer [25]. Although other aetiopathogenetic factors are likely to be involved in this process, infection with *H. pylori* is associated with a 9-fold increased risk for gastric cancer [18,25]. Similar to gastric cancer, the development of oesophageal carcinomas is a multistep sequence in which Barrett's oesophagus, in particular the intestinal type, is a commonly accepted precursor [26]. Although cardiac adenocarcinomas show similar epidemiological and histological features to oesophageal adenocarcinomas, our knowledge concerning the sequence of carcinogenesis is limited. Is the development of this type of carcinoma comparable with the multistep sequence of gastric or oesophageal carcinomas? Does *H. pylori* play a role in its development? Molecular analyses do not solve this problem. Comparative genomic hybridisation of oesophageal and cardiac adenocarcinomas reveals, with few exceptions, similar genetic patterns in both groups [27]. Both types of adenocarcinomas are characterised by a loss of the Y chromosome, a gain of chromosome 20 and a loss of chromosome 5, of which the latter are the most common chromosomal abnormalities [27–30]. The studies of Van Dekken and colleagues and El-Rifai and colleagues show that loss of 14q31-32 is characteristic for oesophageal adenocarcinomas, but other studies could not confirm this observation [31–34]. Amplifications, such as 17q12-q21, 8p22-23 and 19p12, have no discriminative power between oesophageal and cardiac adenocarcinomas [31,33,35,36]. Moreover, similar genetic abnormalities may be found in gastric cancers, such as the amplification of 17q12-21, although with a variable prevalence [37,38]. According to Lin and colleagues, the prevalence of micro-satellite instability, which results from the inactivation of mismatch repair genes, is higher in cardiac adenocarcinomas (62.5%) than in gastric cancers (31.9%) [39]. However, other studies have shown that micro-satellite instability in gastric carcinomas is associated with an antral localisation of the tumour [40,41]. Moreover, the study of Yanagi and colleagues showed that micro-satellite instability was infrequent in proximal gastric cancers and as common as in oesophageal adenocarcinomas, in which the overall prevalence of the study population was less than 10% [34]. Furthermore, molecular biological studies have shown a similar prevalence of *p53*-mutations in cardiac and oesophageal cancers, which is higher than in gastric cancers [42,43]. The results of these molecular studies show that, based on their genetic profile, it is impossible to determine the site of origin of oesophageal and cardiac tumours.

Table 5
Clinical data for patients in the presence or absence of a chronic inflammation

	Oesophageal cancer		Cardiac cancer		Gastric cancer	
Chronic inflammation:	Present	Absent	Present	Absent	Present	Absent
Number of cases	51	84	60	47	12	88
Mean age (years)	67	61	63	64	74	67
Range (years)	45–77	32–86	20–85	37–84	30–93	43–84
M/F ratio	6.28	5.46	3	6.83	2	1.38
Size of tumour (cm)	4.02	3.88	6.17	5.56	4.4	6.08
Range of tumour (cm)	1–10	1–10.5	1.3–12	1.3–13	1–15	1.3–16

In order to investigate disease associations and the possible role of *H. pylori*, we aimed to analyse the prevalence of chronic gastritis and *H. pylori* in the gastric mucosa in association with these different types of upper gastrointestinal cancer. Applying the Sydney system to the gastric tissue, taken at a distance from oesophageal, cardiac and gastric cancers, we have shown that chronic gastritis is more common in the latter type of cancer [20]. Although chronic gastritis is more prevalent in cardiac cancers than in oesophageal cancers ($P < 0.007$), the prevalence of chronic inflammation is significantly lower than in gastric cancers ($P < 10^{-6}$). The inflamed mucosa at a distance from the gastric cancers is more frequently infected with *H. pylori* than in the other types of cancer. The significant difference in the prevalence of chronic gastritis between oesophageal and cardiac adenocarcinomas was related to a significant difference in *H. pylori* colonisation ($P < 0.05$). However, some cases showed gastritis without the presence of *H. pylori*. In our study, we cannot exclude a failure to detect *H. pylori* for technical reasons, as the presence of these micro-organisms has been evaluated on samples of resection specimens and this is known to result in false-negatives. We also cannot exclude that our patients may have received an eradication therapy. However, although *H. pylori* cannot be detected after eradication therapy, the features of the gastritis point towards an infection in the past. Eradication therapy may cause some changes in the histological pattern of the gastritis, in which these alterations are primarily confined to the activity of the gastritis. Although the infiltration of neutrophils will diminish after 6–8 weeks, the regression of the chronic inflammation takes time and will take up to 4 years during which time the antral mucosa will become nearly normal, if it normalises at all [44]. Moreover, if the infection has been present for decades, atrophy and intestinal metaplasia are likely to have developed. Finally, it has not been convincingly shown that atrophy and intestinal metaplasia are reversible [45]. Nevertheless, the prevalence of *H. pylori* found in association with these different types of cancer is comparable with data in the literature [46,47]. Despite the presence of associated *H. pylori* infection, its role in the development of oesophageal and cardiac adenocarcinomas is less clear.

The presence of intestinal metaplasia at the cardia could not be evaluated due to the frequent overgrowth of the tumours at the gastro-oesophageal junction. According to the literature, the prevalence of intestinal metaplasia in the cardia varies between 9 and 31% in patients with a normal squamocolumnar junction (Z-line) [48,49]. Different studies have concluded that the presence of intestinal metaplasia is either related to *H. pylori* infection or to gastro-oesophageal reflux [16,50]. Clearly, the most important argument against a role for *H. pylori* in carcinogenesis in the columnar-lined oesophagus and cardia is the divergence between the decline of the *H. pylori* colonisation rates and the rising prevalence of both types of cancer [4,51].

In this study and in daily clinical practice, we classify our carcinomas situated at the gastro-oesophageal junction as being either of oesophageal or cardiac origin, based on the presence of a Barrett's oesophagus and the location of the bulk of the tumour. Although the advice of the UICC may simplify the problem of classification of gastro-oesophageal tumours, some cases may be misclassified, for example, the associated Barrett's oesophagus may have disappeared in the cases with a large tumour [22]. An argument in favour of this may be the differences in the male/female ratios between those cardiac adenocarcinomas without a chronic inflammation (M/F = 6.83) and those with an inflamed mucosa (M/F = 3) (Table 5). Moreover, this could suggest a heterogeneous composition.

Similar to data in the literature concerning gastric cancer, the prevalence of the gastritis varied with the histological type of carcinoma, as it was more common in association with the intestinal type of adenocarcinomas (Table 4) [52]. However, despite the significant difference in the prevalence of *H. pylori* colonisation between oesophageal and cardiac adenocarcinomas ($P < 0.05$), 44% of cardiac adenocarcinomas are surrounded by a mucosa without any sign of inflammation, which is significantly higher than in the gastric adenocarcinomas ($P < 10^{-6}$). This suggests that the histogenesis of cardiac adenocarcinomas is multifactorial and that *H. pylori* infection is only one of the factors involved. Another factor may be gastro-oesophageal reflux, as the study of Chow and colleagues has shown

that, similar to oesophageal adenocarcinomas, the gastro-oesophageal reflux is associated with a 2-fold higher risk for cardiac adenocarcinomas [53]. The risk of developing cancer is dependent on the composition of the refluxate, as it is known that bile salts are the noxious component in refluxed duodenal juice. Bile reflux in the stomach is a known cause of intestinal metaplasia and gastropathy or reactive gastritis [54].

Up until now, cardiac adenocarcinomas have been staged according to the TNM classification for gastric tumours. In view of the data in the literature on the aetiopathogenesis of cardiac adenocarcinomas, further supported by our data here, new classifications have been proposed along the lines of those for adenocarcinomas situated at the gastro-oesophageal junction. In accordance with these classifications, which aim to evaluate the prognosis of cardiac adenocarcinomas, these cancers are a separate category of gastro-oesophageal adenocarcinomas [55–58].

Acknowledgements

We gratefully acknowledge Prof. Dr. M. Dixon for his help in the preparation of this manuscript.

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