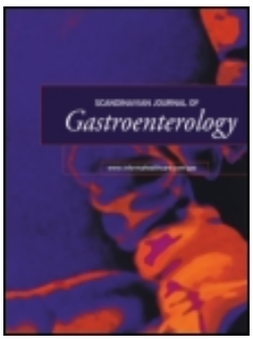

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ORIGINAL ARTICLE

Pathology findings and validation of gastric and esophageal cancer cases in a European cohort (EPIC/EUR-GAST)

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Abstract

Objective. Cardia, non-cardia and intestinal and diffuse subtypes of gastric cancer may have different trends and etiological factors. However, the available information is not always collected in population cancer registries, and heterogeneous criteria have been applied for the histopathological classification of tumors. We describe the pathological features of incident gastric and esophageal cancers identified within the European Prospective Investigation into Cancer and Nutrition (EPIC). ***Material and methods.*** In an investigation on gastric and esophageal cancer (EUR-GAST) in the EPIC project, a validation study of diagnoses reported by EPIC centers was conducted by a European panel of pathologists. Original pathology reports, stained slides of tumors and the respective paraffin blocks were requested from the centers. ***Results.*** The whole series encompassed 467 cancer cases (gastric and esophageal cancers). Material was available for histopathological validation in 263 cases (56%); in the remaining cases, information was retrieved from the original reports ($n=110$; 24%) or codes provided by the EPIC centers ($n=94$; 20%). Among cases submitted to histopathological validation reported

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originally as unknown histotype or unknown site, a specific diagnosis was made in 95% and 74% of the cases, respectively. In cases for which only the original reports were available, the respective percentages were 46% and 67%. Gastric adenocarcinomas were classified according to site (cardia (29.4%), non-cardia (48.2%) and unknown (22.4%)) and histological type (intestinal (33.4%), diffuse (33.7%) and mixed, unclassified or unknown (32.9%)). Frequency of cardia was higher in Northern countries (35%) than in Mediterranean countries (18%). ***Conclusions.*** In addition to providing epidemiological data within the EPIC cohort on gastric and esophageal adenocarcinomas, the results reported here confirm the relevance of a validation study, notably for multicenter studies.

Key Words: *EPIC, epidemiology, esophageal cancer, EUR-GAST, gastric cancer, pathology, validation study*

Introduction

Overall, gastric and esophageal cancers are, respectively, the second and sixth most common causes of death in the world [1]. Gastric cancer is a major public health problem in several European countries. Across Europe, there are major differences in the incidence of gastric cancer, higher rates being registered in central and Eastern Europe, as well as in Portugal, Spain and Italy. In the past few decades, a decline has been observed in gastric cancer incidence and mortality in most European countries. The reasons underlying these observations are complex and not well understood. According to site, gastric cancer encompasses two major types: cardia and non-cardia adenocarcinomas. Incidence of gastric cardia cancer has risen steadily in the United States [2] and Europe [3] in parallel with the rising incidence of esophageal adenocarcinomas [1]. By contrast, the incidence of gastric non-cardia cancer has declined in most countries [1]. These different trends could be related to changing risk factors. *Helicobacter pylori* infection is an established risk factor for non-cardia gastric cancer but is not associated with the cardia site [4], while tobacco smoking [5] and diet are associated with both. Gastroesophageal reflux disease and obesity are known risk factors for cardia/proximal gastric cancer and esophageal adenocarcinomas [6].

In this study, we describe the pathological features of incident gastric and esophageal cancers (adenocarcinomas) identified within the European Prospective Investigation into Cancer and Nutrition (EPIC), a large prospective European cohort, reported in full elsewhere [7,8]. A nested case-control study was developed within the EPIC cohort, focusing on the analysis of risk factors for gastric and esophageal cancer development. This specific study was funded by the European Commission (EUR-GAST).

The aims of the pathology study in the frame of the EPIC/EUR-GAST cohort were: (a) To validate the pathological diagnoses of gastric and esophageal cancers (adenocarcinomas) included in the EUR-GAST study, and to classify the cases according to accepted histopathological classifications; and (b) to confirm the anatomical localization of gastric cancer cases.

Material and methods

EPIC is a multicenter prospective study coordinated by the International Agency for Research on Cancer (IARC, Lyon, France) with the aim of investigating the association between diet and lifestyle habits and cancer, based on healthy adults who voluntarily agreed to participate in the study and to have their health status followed-up. The enrolment started in 1992–93 and was completed in 1998 in 23 collaborating centers in 10 European countries (Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, The Netherlands and the UK). Overall, approximately 520,000 subjects (F – 71%, M – 29%), mostly aged 35–74 years, have been recruited.

The study design has been reported in full elsewhere [7,8]. Briefly, the volunteers were mostly enrolled from the general population residing in a specific area. Exceptions were the French cohort, based on female members of a national health insurance for schoolteachers and the Utrecht cohort (The Netherlands) based on women attending the local breast cancer screening program. The five Spanish cohorts and the Italian cohorts in Ragusa and Turin were based mainly on blood donors; most of the Oxford cohort in the UK comprised vegetarian and health-conscious volunteers recruited from across the whole country.

The design of the study encompassed the validation of the gastric and esophageal cancer diagnoses reported to the IARC within the EPIC cohort. For that purpose, a European panel of pathologists was established, led by eight pathologists from different participating countries, and a coordinator (F.C.).

The members of the panel of pathologists were involved in the following specific tasks: (a) to obtain, in each country, the collaboration from the Pathology Departments for the diagnosis of incident gastric and esophageal cancer cases within the EPIC cohort; the coordinator of the EPIC center assisted the pathologist in this work; (b) to discuss the operative guidelines for diagnosis of cases, harmonization of classification and nomenclature (a protocol was prepared by the coordinator of the panel of pathologists); (c) to review the histological type and anatomical localization of all cases; (d) to collect

pathologic material of the cases from his/her country that was used in the revision process and sent to the central coordinator (F.C.). The coordinator reviewed all material received from the different countries. Material requested for the revision of cases was the following: the original pathology report, protocol prepared for the study (completed by pathologists in each country), one or two hematoxylin-eosin (H&E) stained slides representative of the tumors and one or two paraffin blocks from which new cuts were obtained. Whenever there was agreement between the coordinator and pathologists in each country, the diagnoses were validated; whenever there was any disagreement, cases were selected for a validation study conducted by the members of the panel of pathologists during a meeting held in Porto. At this meeting, individual diagnoses were evaluated in a second look using a multiheaded microscope and all available information provided by each country. Final diagnoses were reached by consensus among the participating members of the panel of pathologists.

Whenever material was not available for histopathological validation, original reports obtained from the centers were carefully reviewed in order to validate the information that had been reported to the IARC by the EPIC centers. This exercise was invaluable in obtaining more precise information on cases reported to the IARC simply as "Stomach NOS" or "carcinoma/adenocarcinoma NOS" regarding site and/or histotype, respectively.

Gastric adenocarcinomas were classified according to the classifications of Lauren (intestinal, diffuse, mixed and undetermined/unclassified) and Carneiro (glandular, isolated-cell type, mixed and solid) [9–11]. Cases in which it was not possible to apply Lauren's classification were coded as "adenocarcinomas, unknown", corresponding to adenocarcinomas not otherwise specified (NOS).

Cancers developed around the gastroesophageal junction (GEJ) were classified as: esophageal adenocarcinomas (developing entirely above the GEJ), GEJ adenocarcinomas (tumors crossing the GEJ, and without evidence of developing in Barrett's mucosa) and gastric adenocarcinomas reaching (without crossing) the GEJ [12]. GEJ was defined as the proximal end of the gastric folds (at macroscopy) or by the proximal limit of the gastric oxyntic mucosa (by histology) [13]. For the purpose of the present study, tumors crossing the GEJ and those developing just below it were grouped in a broad group of "cardia" carcinomas.

Cases in which it was not possible to determine the precise localization of the tumors were coded, as per site, as "site unknown".

According to the requirements of the study, no material was provided from non-neoplastic mucosa. It was therefore not possible to characterize the background changes of gastric mucosa.

The χ^2 and the Fisher exact tests were used to test for an association between categorical variables, while ANOVA was used to compare the age of patients between several categories.

Results

Features of the whole series and results of the validation study

The whole list of cases provided by the IARC comprised 486 cases. Nineteen cases were excluded for the following reasons: 7 cases were censored by date of diagnosis; 4 cases were dysplastic lesions with no evidence of invasive cancer; 2 cases corresponded to metastases; 6 cases were non-adenocarcinoma cancer of the esophagus.

The remaining 467 cases provided by each participating country are represented in Figure 1, corresponding to Northern countries ($n=329$) and Mediterranean countries ($n=138$). Among the 467 cases, material was obtained for histopathological validation by the panel of pathologists in 263 cases (56%); in 110 cases (24%) only the original reports were provided by the centers; in the remaining cases, information was obtained by codes directly provided by the centers ($n=80$; 17%) or codes provided by the IARC (originally reported to the IARC by the centers) ($n=14$; 3%). Figure 2 shows the distribution of cases per country according to the sources of information.

Cases submitted to histopathological validation ($n=263$) encompassed cases reported to the IARC as gastric tumors ($n=210$) and esophageal tumors ($n=53$) (Tables I and II). Fourteen cases originally reported to the IARC as esophageal adenocarcinomas were moved to the cardia tumor group; 3 cases originally reported to the IARC as cardia tumors were moved to the esophagus group (Table I). Cases from which information was retrieved only from the original reports ($n=110$) encompassed cases reported to the IARC as gastric tumors ($n=100$) and esophageal tumors ($n=10$) (Tables III and IV). Two cases originally reported to the IARC as esophageal adenocarcinomas were moved to the cardia tumor group; 2 cases originally reported to the IARC as gastric tumors (1 cardia and 1 gastric unknown) were moved to the esophagus group (Table III).

The whole series ($n=467$) (276 M, 191 F) encompassed adenocarcinomas of the lower esophagus ($n=67$), gastric adenocarcinomas ($n=355$),

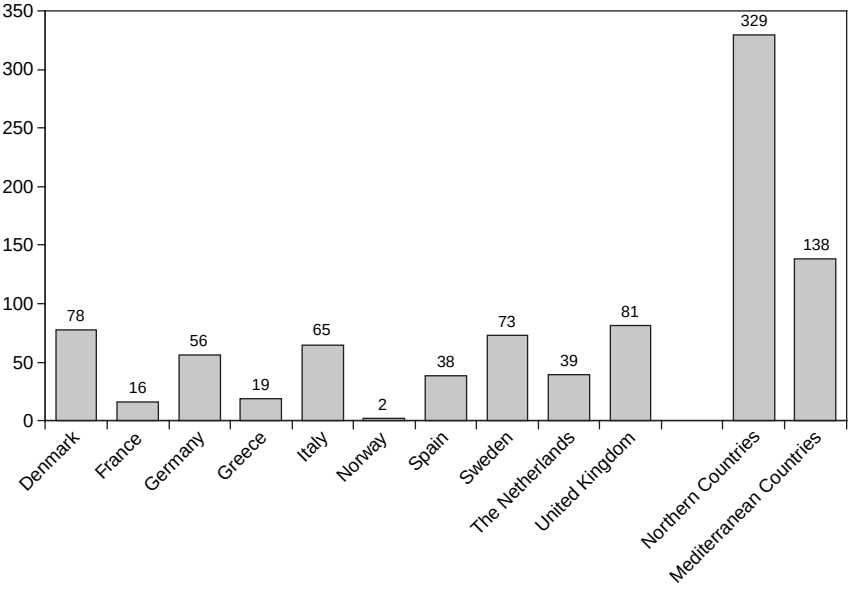

Figure 1. Distribution of cases according to country of origin and Northern versus Mediterranean countries.

lymphomas ($n=26$), malignant neoplasms NOS ($n=8$) and a group of "other tumor types" ($n=11$, including 4 neuroendocrine carcinomas, 6 gastrointestinal stromal tumors (GISTs) and one leiomyosarcoma).

Features of gastric adenocarcinomas

Gastric adenocarcinomas ($n=355$) encompassed tumors crossing the GEJ ($n=24$) and adenocarcinomas developing entirely in the stomach ($n=331$), the latter group encompassing tumors reaching the GEJ without crossing it ($n=77$), tumors developing in the distal stomach ($n=166$), tumors from which it was not possible to obtain precise information on localization (unknown site; $n=77$), tumors developing in more than one anatomic region (mixed site; $n=6$) and tumors developing in the gastric stump ($n=5$).

For the purpose of statistical analysis, gastric stump and mixed-site tumors ($n=11$) were not used. The remaining 344 cases (198 M, 146 F) were grouped as follows: cardia adenocarcinomas ($n=101$; 29.4%) (encompassing 24 adenocarcinomas crossing the GEJ and 77 adenocarcinomas reaching the GEJ without crossing it); non-cardia adenocarcinomas ($n=166$; 48.2%) and adenocarcinomas whose precise site was not known ($n=77$; 22.4%).

Cardia adenocarcinoma was found more frequently among men (37%) than among women

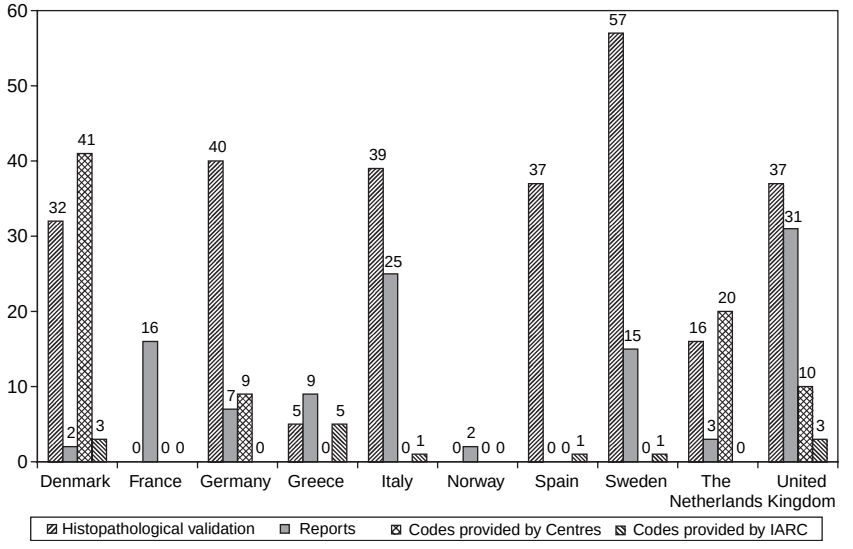

Figure 2. Distribution of cases per country, according to the source of information. IARC = International Agency for Research on Cancer.

Table I. Distribution of the localization of gastric and esophageal tumors using the original information reported by the EPIC centers to the IARC and the final classification of the panel of pathologists.

		Final classification of the panel of pathologists						
		Esophageal adenocarcinoma *n* (%)	[a]Cardia *n* (%)	Non-cardia *n* (%)	[b]Mixed site *n* (%)	[c]Gastric unknown *n* (%)	Gastric stump *n* (%)	Total *n* (%)
ORIGINAL INFORMATION PROVIDED BY EPIC CENTERS	Esophageal adenocarcinoma	39 (74)	14 (26)	0	0	0	0	53 (100)
	Cardia	3 (10)	24 (83)	2 (7)	0	0	0	29 (100)
	Non-cardia	0	5 (7)*	54 (79)**	0	8 (12)****	1 (2)	68 (100)
	[b]Mixed site	0	0	9 (100)	0	0	0	9 (100)
	[c]Gastric unknown	0	12 (12)	56 (54)***	6 (6)	27 (26)	3 (3)	104 (100)
	Total	42 (16)	55 (21)	121 (46)	6 (2)	35 (13)	4 (2)	263 (100)

Abbreviations: EPIC = European Prospective Investigation into Cancer and Nutrition; IARC = International Agency for Research on Cancer.
*Includes 1 neuroendocrine tumor; **includes 1 lymphoma, 1 neuroendocrine tumor and 3 sarcomas; ***includes 9 lymphomas and 1 sarcoma; ****includes 2 lymphomas and 1 neuroendocrine tumor.
[a]Cardia cases encompass tumors crossing the gastroesophageal junction (GEJ) and tumors reaching the GEJ without crossing it; [b]Tumors in more than one anatomic region (cardia and non-cardia); [c]Tumors for which it was not possible to obtain precise information on localization.

(18%) while non-cardia adenocarcinoma was more frequent among women (58%) than among men (41%) and similar frequencies of adenocarcinoma of unknown site were observed among men (21%) and women (24%) ($p = 0.0004$). No significant difference was observed regarding the age of patients according to the different localizations of the tumors: cardia adenocarcinomas (63.8 ± 7.4), non-cardia adenocarcinomas (62.5 ± 8.5) and adenocarcinomas of unknown site (63.5 ± 8.5) ($p = 0.43$).

Among gastric adenocarcinomas significant differences in histotypes were observed according to site (cardia, non-cardia and unknown) ($p < 0.0001$) (Table V).

Patients with intestinal carcinomas were older (64.0 ± 7.3) than patients with diffuse carcinomas (60.4 ± 8.7) ($p = 0.001$). Significant differences were observed also regarding the gender of patients. Intestinal carcinomas were the most frequent among men (39%) while diffuse carcinomas were the most frequent among women (44%) ($p = 0.01$). Site and histological type were analyzed according to countries in the subgroup of 344 gastric adenocarcinomas, as shown in Table VI. In the Northern countries, 235 gastric adenocarcinomas were identified, and classified according to site as cardia ($n = 81$; 35%), non-cardia ($n = 106$; 45%) and unknown site ($n = 48$; 20%). In the Mediterranean countries, 109 gastric adenocarcinomas were identified, and classified as cardia ($n = 20$; 18%), non-cardia ($n = 60$; 55%) and unknown site ($n = 29$; 27%). These differences were statistically significant ($p = 0.009$). No significant differences ($p = 0.28$) were observed among countries regarding histological type (Laurén's classification).

Carneiro's classification was applied in a subgroup of 184 gastric adenocarcinomas, for which there was material for histopathological validation within the group of 344 gastric adenocarcinomas, as defined above. Cases were classified as follows: glandular ($n = 83$; 45.1%), isolated cell-type ($n = 67$; 36.4%), mixed ($n = 25$; 13.6%) and solid ($n = 9$; 4.9%) carcinomas. Glandular carcinomas were found most frequently among men (54%) while isolated cell-type were the most frequent carcinomas among women (51%) ($p = 0.003$). A significant relationship was observed between tumor site and histotypes according to Carneiro's classification ($p = 0.01$): cardia adenocarcinomas were predominantly glandular carcinomas (60%), followed by isolated cell-type (17%), mixed (19%) and solid (4%) carcinomas; non-cardia adenocarcinomas were classified as glandular (41%), isolated cell-type (39%), mixed (13%) and solid (7%) carcinomas; tumors whose site was unknown were predominantly isolated cell-type carcinomas (56%), followed by glandular (34%) and

Table II. Distribution of the histotypes of gastric and esophageal tumors using the original information reported to the IARC by the EPIC centers and the final classification of the panel of pathologists.

			Final classification of the panel of pathologists							
			Gastric adenocarcinoma							
			Intestinal *n* (%)	Diffuse *n* (%)	Mixed *n* (%)	Unclassified *n* (%)	Unknown n (%)	Gastric non-adenocarcinoma *n* (%)	Malignant neoplasm *n* (%)	Esophageal adenocarcinoma *n* (%)	Total *n* (%)
ORIGINAL INFORMATION PROVIDED BY EPIC CENTERS	Gastric adenocarcinoma	Intestinal	19 (95)	0	0	1 (5)	0	0	0	0	20 (100)
		Diffuse	1 (2)	40 (93)	0	1 (2)	1 (2)	0	0	0	43 (100)
		Mixed	1 (100)	0	0	0	0	0	0	0	1 (100)
		Unclassified	0	0	0	0	0	0	0	0	0
		Unknown	61 (49)	46 (37)	1 (1)	8 (6)	6 (5)	0	0	3 (2)	125 (100)
	Gastric non-adenocarcinoma		0	0	0	1 (5)	0	19 (95)*	0	0	20 (100)
	Malignant neoplasm		0	1 (100)	0	0	0	0	0	0	1 (100)
	Esophageal adenocarcinoma		8 (15)	0	2 (4)	0	4 (8)	0	0	39 (74)	53 (100)
	Total		90 (34)	87 (33)	3 (1)	11 (4)	11 (4)	19 (7)	0	42 (16)	263 (100)

Abbreviations: EPIC = European Prospective Investigation into Cancer and Nutrition; IARC = International Agency for Research on Cancer.
*Includes 12 lymphomas, 4 sarcomas and 3 neuroendocrine tumors.

mixed carcinomas (9%). No significant intercountry differences were observed in the proportion of histotypes according to Carneiro's classification ($p = 0.42$).

Features of esophageal adenocarcinomas

The subgroup of esophageal adenocarcinomas comprised 67 cases (24 of these cases were classified as Barrett's type adenocarcinomas on the basis of features of non-neoplastic mucosa adjacent to the tumors, displaying features of intestinal metaplasia; it cannot be ruled out that a proportion of the other 43 esophageal adenocarcinomas were Barrett's adenocarcinomas which we could not diagnose because of the lack of non-neoplastic mucosa). In the present series, all esophageal adenocarcinomas displayed glandular structure.

Esophageal adenocarcinomas developed in 50 men (75%) and 17 women (25%). Mean age of the patients was 65.3 ± 8.0 (minimum – 44; maximum – 81). In relation to countries, 65 (97%) of esophageal adenocarcinomas developed in the Northern countries (Denmark – 21 cases; Germany – 2 cases; Sweden – 13 cases; The Netherlands – 4; United Kingdom – 25) and 2 (3%) of the cases developed in the Mediterranean countries (Italy – 2).

Discussion

An appropriate definition of any disease that is being studied is critical for large epidemiological studies that focus on etiological factors. Histopathological revision may be a precondition, and in the case of investigations of the cause of carcinomas, this is in fact always true. Interestingly, gastric cancer is one of the specific carcinomas where one of the original classification systems (Lauren's classification) [9] already reflected the close association between the epidemiology and histopathology. Lauren's classification is still used and distinguishes between two main histological types of stomach cancer based on morphology and growth pattern – diffuse and intestinal types – with distinct epidemiological profiles. This illustrates nicely the significance of proper classifications for epidemiological research. The reporting of our recent experience with the review of the cases included in a large international collaborative epidemiological prospective study on the etiology of stomach cancer is intended to draw attention to the importance of this often painstaking and time-consuming process and it may at the same time provide useful guidelines for other studies of this kind in the future.

Table III. Distribution of the localization of gastric and esophageal tumors using the original information reported by the EPIC centers to the IARC and the classification retrieved from the original reports.

		Classification retrieved from original reports						
		Esophageal adenocarcinoma *n* (%)	[a]Cardia *n* (%)	Non-cardia *n* (%)	[b]Mixed site *n* (%)	[c]Gastric unknown *n* (%)	Gastric stump *n* (%)	Total *n* (%)
ORIGINAL INFORMATION PROVIDED BY EPIC CENTERS	Esophageal adenocarcinoma	8 (80)	2 (20)	0	0	0	0	10 (100)
	Cardia	1 (5)	18 (90)*	1 (5)	0	0	0	20 (100)
	Non-cardia	0	0	17 (85)***	0	3 (15)	0	20 (100)
	[b]Mixed site	0	0	0	0	0	0	0
	[c]Gastric unknown	1 (2)	8 (13)**	30 (50)****	0	20 (33)*****	1 (2)	60 (100)
	Total	10 (9)	28 (25)	48 (44)	0	23 (21)	1 (1)	110 (100)

Abbreviations: EPIC = European Prospective Investigation into Cancer and Nutrition; IARC = International Agency for Research on Cancer.
*Includes 1 lymphoma; **includes 1 sarcoma; ***includes 4 lymphomas; ****includes 1 lymphoma and 1 sarcoma; *****includes 3 malignant neoplasms and 1 sarcoma.
[a]Cardia cases encompass tumors crossing the gastroesophageal junction (GEJ) and tumors reaching the GEJ without crossing it; [b]tumors in more than one anatomic region (cardia and non-cardia); [c]tumors for which it was not possible to obtain precise information on localization.

Table IV. Distribution of the histotypes of gastric and esophageal tumors using the original information reported by the EPIC centers to the IARC and the classification retrieved from the original reports.

			Classification retrieved from original reports								
			Gastric adenocarcinoma								
			Intestinal *n* (%)	Diffuse *n* (%)	Mixed *n* (%)	Unclassified *n* (%)	Unknown *n* (%)	Gastric non-adenocarcinoma *n* (%)	Malignant neoplasm *n* (%)	Esophageal adenocarcinoma *n* (%)	Total *n* (%)
ORIGINAL INFORMATION PROVIDED BY EPIC CENTERS	Gastric adenocarcinoma	Intestinal	14 (100)	0	0	0	0	0	0	0	14 (100)
		Diffuse	0	11 (100)	0	0	0	0	0	0	11 (100)
		Mixed	0	0	0	0	0	0	0	0	0
		Unclassified	0	0	0	0	0	0	0	0	0
		Unknown	11 (17)	13 (21)	1 (2)	2 (3)	34 (54)	0	0	2 (3)	63 (100)
	Gastric non-adenocarcinoma		0	0	0	0	0	9 (100)*	0	0	9 (100)
	Malignant neoplasm		0	0	0	0	0	0	3 (100)	0	3 (100)
	Esophageal adenocarcinoma		0	0	0	0	2 (20)	0	0	8 (80)	10 (100)
	Total		25 (23)	24 (22)	1 (1)	2 (2)	36 (33)	9 (8)	3 (3)	10 (9)	110 (100)

Abbreviations: EPIC = European Prospective Investigation into Cancer and Nutrition; IARC = International Agency for Research on Cancer.
*Includes 6 lymphomas and 3 sarcomas.

Table V. Distribution of histotypes (Laurén's classification) according to site.

	Histological type					
Localization	Intestinal *n* (%)	Diffuse *n* (%)	Mixed *n* (%)	Unclassified *n* (%)	Unknown *n* (%)	Total *n* (%)
Cardia adenocarcinoma	42 (42)	18 (18)	2 (2)	4 (4)	35 (35)	101 (100)
Non-cardia adenocarcinoma	58 (35)	64 (39)	2 (1)	10 (6)	32 (19)	166 (100)
Unknown site	15 (20)	34 (44)	0 (0)	0 (0)	28 (36)	77 (100)
Total	115 (33)	116 (34)	4 (1)	14 (4)	95 (28)	344 (100)

In the present study, a panel of pathologists was involved in a validation study of histology and site of gastric and esophageal (adeno)carcinomas. The results presented here show that after the revision made by the panel of pathologists, a precise histological classification was provided for 95% of the cases reported to the IARC as "gastric, unknown", and 74% of the cases reported to the IARC as site unknown were allocated to precise localizations. Furthermore, the revision of original reports allowed a better classification of 46% of the cases originally reported to the IARC as unknown according to histological type and 67% of the cases reported as unknown according to site. These results show that the histopathological validation leads to improvement of the original reported data to a higher level than the revision of the original histological reports.

Owing to restrictive rules for availability of patient tissues, two countries did not contribute cases for the histopathological validation study, which may constitute an important shortcoming in this type of study. Awareness of this and other shortcomings, such as the type of recruited populations in some countries, is the reason for our cautious interpretation of the findings of this study.

Another major limitation is the lack of uniformity of reporting from different pathologists and the difficulty in or even impossibility of obtaining detailed data on the topography of the tumors, which has a direct impact on the classification systems based on the location of the tumors. This is the case with tumors developing around the GEJ, for which two major classifications have been proposed: Siewert & Stein [14] and the WHO classifications [12]. In Siewert's classification, the tumors are classified according to the localization of the main tumor mass, in relation to the anatomical cardia, defined for this purpose as the proximal end of the gastric fold: adenocarcinomas of the esophagus (AGE I), as tumors located in the esophagus, more than 1 cm above the anatomical GEJ and that may infiltrate the GEJ from above; true "junctional" carcinomas (AGE II), as tumors extending 1 cm above and 2 cm below the anatomic GEJ; subcardiac gastric cancers (AGE III), as tumors located more than 2 cm below the anatomical GEJ and that may infiltrate the GEJ and the distal esophagus from below. The scarcity/lack of precise information on tumor epicenters precluded the use of this classification in the present study. Alternatively, the panel of pathologists took into consideration some of the recommendations of WHO classification to classify tumors around the GEJ as follows: esophageal adenocarcinomas (developing entirely above the GEJ), GEJ adenocarcinomas (tumors that cross the GEJ) and (proximal) gastric adenocarcinomas (developing entirely below the GEJ). For the purpose of the present study, tumors crossing the GEJ and those developing just below it were grouped in a broad group of "cardia" carcinomas and distinguished from those developing in other anatomic regions of the stomach (non-cardia carcinomas) and in the lower esophagus (esophageal adenocarcinomas).

According to Lauren's classification, gastric adenocarcinomas were classified as intestinal (33%), diffuse (34%), mixed (1%) and unclassified/undetermined (4%). Patients with intestinal carcinomas were significantly older than those with diffuse carcinomas. Intestinal carcinomas were found most frequently among men while diffuse carcinomas were the most frequent among women. These observations are in accordance with the well-known features of the two main types of gastric cancer as reported in the literature [15].

Besides Lauren's classification [9], we also applied the classification proposed by Carneiro et al. [10]. A concordance was observed between major histotypes in both classifications (intestinal versus glandular and diffuse versus isolated cell-type carcinomas). The frequency of cases classified as mixed carcinomas according to Carneiro's classification was lower than that observed in previous studies [10,16,17]. This discrepancy may be due to the small number of samples observed in the present study (one or two sections, while the original Carneiro's classification recommends the observation of five sections for a precise identification of mixed carcinomas). Despite

Table VI. Distribution of tumor site and main histotypes (intestinal and diffuse) of Laurén's classification, according to countries (in a subgroup of 344 gastric adenocarcinomas).

Countries	Number of cases	Localization			Histological type				
		Cardia *n* (%)	Non-cardia *n* (%)	Unknown *n* (%)	Intestinal *n* (%)	Diffuse *n* (%)	Mixed *n* (%)	Unclassified *n* (%)	Unknown *n* (%)
Denmark	52	24 (46)	16 (31)	12 (23)	13 (25)	7 (13)	2 (4)	3 (6)	27 (52)
France	11	4 (36)	4 (36)	3 (27)	3 (27)	3 (27)	0 (0)	0 (0)	5 (46)
Germany	41	10 (24)	24 (59)	7 (17)	15 (37)	20 (49)	1 (2)	1 (2)	4 (10)
Greece	16	2 (13)	4 (25)	10 (63)	4 (25)	9 (56)	0 (0)	0 (0)	3 (19)
Italy	50	8 (16)	31 (62)	11 (22)	25 (50)	15 (30)	0 (0)	4 (8)	6 (12)
Norway	2	0 (0)	0 (0)	2 (100)	0 (0)	1 (50)	0 (0)	0 (0)	1 (50)
Spain	32	6 (19)	21 (66)	5 (16)	13 (41)	13 (41)	1 (3)	3 (9)	2 (6)
Sweden	59	17 (29)	34 (58)	8 (14)	23 (39)	27 (46)	0 (0)	3 (5)	6 (10)
The Netherlands	29	9 (31)	9 (31)	11 (38)	6 (21)	12 (41)	0 (0)	0 (0)	11 (38)
United Kingdom	52	21 (40)	23 (44)	8 (15)	13 (25)	9 (17)	0 (0)	(0)	30 (58)
Total	344	101 (29)	166 (48)	77 (22)	115 (33)	116 (34)	4 (1)	14 (4)	95 (28)

this shortcoming, it is interesting to note that the frequency of mixed carcinomas was higher in cardia tumors than in non-cardia tumors (19% versus 13%, respectively), in line with studies previously reported [10,16]. Although the epidemiology of mixed carcinomas has not yet been clarified, it is worth emphasizing the relevance of this tumor type for prognosis, especially in cardia tumors, since this tumor type has a negative bearing on survival of the patients [16].

In the Northern countries, the frequency of cardia tumors (35%) was higher than that in the Mediterranean countries (18%), in keeping with an increase in cardia carcinoma observed in some Northern countries [18]. However, high variability was observed among different countries in accordance with the data on record [19]. No significant differences were observed in histotypes in the comparison of Northern and Mediterranean countries.

Among non-cardia adenocarcinomas, the diffuse histotype was the most frequent, in contrast to cardia adenocarcinomas in which the intestinal histotype was the most frequent. Some studies point to a progressive decrease in the incidence of the intestinal type of gastric cancer and an increase in the diffuse type of gastric carcinoma [15,20], whereas a large population-based study in Sweden showed no significant differences in trend between the intestinal and diffuse histotypes [21]. Our study does not allow for analysis of the time trend of the different histotypes of gastric cancer, but we suggest that in the case of a decrease in intestinal carcinoma occurring in European countries this affects mainly non-cardia adenocarcinoma.

The demographic features of esophageal adenocarcinomas were compared with those of cardia and non-cardia adenocarcinomas. Patients with esophageal adenocarcinomas were significantly older than patients with cardia and non-cardia adenocarcinomas. Frequency of male gender was significantly higher in esophageal and cardia adenocarcinomas than in non-cardia adenocarcinomas, in keeping with data elsewhere [17,22]. A relevant finding is that most esophageal adenocarcinomas were identified in Northern countries.

In conclusion, besides providing some epidemiological data within the EPIC cohort of gastric and esophageal adenocarcinomas, the results reported here show the relevance of the histopathological validation study which, in our view, is fundamental for multicenter studies on gastric and esophageal cancer.

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