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ORIGINAL ARTICLE

Gastric cancer: Decreasing incidence but stable survival in the Netherlands

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Abstract

Background. Gastric cardia and non-cardia cancer exhibit differences in biological and epidemiological features across the world. The aims of this study were to analyze trends in incidence, stage distribution, and survival over a 20-year period in the Netherlands, separately for both types of gastric cancer. *Methods.* Data on all patients with a diagnosis of gastric cancer in the period 1989–2008 were obtained from the nationwide Netherlands Cancer Registry. Time trends in incidence [analyzed as European Standard Rate per 100 000 (ESR)] and relative survival were separately analyzed for cardia and non-cardia gastric cancer. *Results.* A total of 47 295 patients were included. Incidence rates per 100 000 for cardia cancer declined from 5.7 to 4.3 for males and remained stable for females (1.2). For non-cardia cancer, the incidence in males declined from 25 to 14 and in females from 10 to 7. Proportional incidence in stage IV cardia and non-cardia cancer increased in 2004–2008 (cardia 32–42%, non-cardia 33–45%). Five-year survival rates for stage I–III and X (unknown) remained stable (cardia cancer: 20%, non-cardia gastric cancer: 31%). Five-year survival for stage IV disease was 1.9% and 1.0% for cardia and non-cardia gastric cancer. *Conclusion.* The incidence of gastric cancer in the Netherlands markedly decreased over the past decades, in particular of non-cardia cancer. Survival remained dismal. Improvement of survival remains a challenge for the multidisciplinary team involved in gastric cancer treatment.

Gastric cancer can be subdivided in two distinct forms according to location, i.e. gastric cardia cancer and gastric non-cardia cancer. These two entities are reported to show different epidemiological and biological behavior. The declining incidence in gastric cancer [1] throughout the world is mostly attributed to a fall in incidence of non-cardia cancer [2,3]. The literature on incidence rates of cardia cancer is somewhat conflicting, with decreasing, stable and increasing incidence rates reported [2–6]. This is in contrast to adenocarcinoma of the distal esophagus which has increased markedly [2,4,6].

Survival of gastric cancer remains dismal in the Western world, with reported five-year survival rates of 10–30% [1], in contrast to Asian survival rates (69%) [7]. The latter has been attributed to the availability of screening programs, more aggressive surgery, differences in staging, and an intrinsic biological difference between Asian and Western gastric cancer patients [8,9]. In both Western and Asian countries survival of cardia gastric cancer is lower compared to non-cardia cancer [5,7].

In this paper, the results of this nationwide population-based study on incidence and survival rates for gastric cancer in the Netherlands are presented. Trends in incidence, mortality, stage distribution, and survival rates for cardia and non-cardia gastric cancer were evaluated, over a period of 20 years.

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Methods

Data collection

Data were obtained from the nationwide Netherlands Cancer Registry (NCR). This registry serves the total Dutch population of 16.6 million inhabitants. The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the automated pathological archive (PALGA). Additional sources are the national registry of hospital discharge, hematology departments and radiotherapy institutions. Completeness is estimated to be at least 95% [10]. The information on vital status was initially obtained from municipal registries and from 1994 onwards from the nationwide population registries network. Both these registries provide complete coverage of all deceased Dutch citizens. Disease-specific mortality rates were obtained from Statistics Netherlands (CBS).

Patients diagnosed from 1989 to 2008 with a tumor of the stomach, classified as ICD-9 151 and ICD-10 C16 according to the International Classification of Diseases (ICD), were included. Tumors were staged according to the International Union Against Cancer TNM classification that was used at the date of diagnosis. Between the 4th and 5th edition TNM classification, the classification was changed for nodal staging. Starting with the 5th edition, nodal (N) status was based on the absolute number of positive lymph nodes, rather than the location of the lymph node metastases. There were no differences between the 5th and 6th edition TNM classification. Clinical stage group was used in case of missing pathological TNM stage group [11–13]. Stage X was assigned to patients with unknown stage. To evaluate trends over time, the study period was divided in four intervals of five years.

Statistical analyses

Annual incidence and mortality rates were calculated per 100 000 person years, using the annual mid-year population size as obtained from Statistics Netherlands. Rates were age-standardized to European Standardized Rates (ESR). Changes were evaluated by calculating the estimated annual percentage change (EAPC) and the corresponding 95% confidence interval. To calculate this, a regression line was fitted to the natural logarithm of the rates, using the calendar year as regressor variable [i.e. $y = ax + b$ where $y = \ln(\text{rate})$ and $x = \text{calendar year}$, then $\text{EAPC} = 100 \times (e^a - 1)$].

TNM stage was calculated by using pathological T, N and M stage. If pathological confirmation was lacking, clinical T, N and/or M stage was used. Analyses were stratified for stage (stage I–III/X vs. stage IV). Differences in stage distribution between periods of diagnosis were tested by means of a χ^2-test.

Follow-up for vital status was complete until 31 December 2009. Traditional cohort-based relative survival analysis was calculated; the number of days was calculated from the date of diagnosis until death of any cause (event) or alive at last follow-up (censored). Then, relative survival was calculated correcting for age- and gender-specific background mortality, as a proxy of disease-specific survival.

SAS software (SAS system 9.2, SAS Institute, Cary, NC, USA) was used to perform the statistical analyses. For all analyses, a p-value < 0.05 was considered significant.

Results

Patient characteristics and incidence

A total of 47 295 patients diagnosed with gastric cancer were included (Table I). The incidence of cardia cancer decreased in males, and remained stable in females. The incidence of non-cardia cancer decreased in both males and females. The median age for both cardia and non-cardia cancer remained stable (Table I).

Age-standardized incidence rates (per 100 000 person years) by gender are shown in Figure 1. The ESR in males decreased from 25/100 000 in 1989 to 14/100 000 in 2008, and decreased in females from

Table I. Age and gender distribution of all patients with gastric cancer.

	Cardia								Non-cardia							
	1989–1993		1994–1998		1999–2003		2004–2008		1989–1993		1994–1998		1999–2003		2004–2008	
Age (years)	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
< 55	382	14	476	16	421	15	413	15	1204	11	1042	11	1037	12	929	12
55–64	636	23	590	20	620	22	600	22	1715	16	1462	16	1370	16	1344	17
65–74	905	33	1006	33	866	31	802	29	3224	30	2757	30	2477	30	2273	29
75+	860	31	933	31	874	31	909	33	4458	42	3867	42	3481	42	3365	43
Gender																
Male	2115	76	2330	78	2080	75	2059	76	6287	59	5338	59	4870	58	4634	59
Female	668	24	675	22	701	25	665	24	4314	41	3790	41	3492	42	3277	41

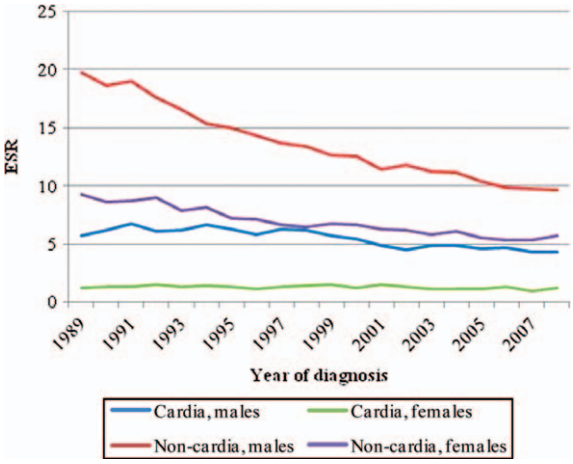

Figure 1. Trends in incidence according to location and gender, the Netherlands 1989–2008. ESR, European Standardized Rate per 100 000 inhabitants.

10/100 000 to 7/100 000. The estimated annual percentage change in incidence was -3.4 (95% CI −3.6 to −3.2) for males, −2.6 (95% CI −2.9 to −2.2) for females, −2.2 (95% CI −2.8 to −1.6) for males with cardia cancer, −0.94 (95% CI −1.9 to −0.02) for females, −3.8 (95% CI −4.1 to −3.6) for males with non-cardia cancer, and −2.9 (95% CI −3.2 to −2.5) for females. Age-standardized mortality rates declined for both men (from 20.8 to 9.2) and women (from 8.2 to 4.3).

Tumor stage

The proportion of patients with stage IV at diagnosis (pathological or clinical) increased for both cardia (from 32% in 1989–1993 to 45% in 2004–2008, $p > 0.0001$) and non-cardia cancer (from 31% in 1989–1993 to 43% in 2004–2008, $p > 0.0001$), with a corresponding decrease in the percentage of patients with an unknown stage (Figure 2a and b).

Survival

Five-year relative survival estimates for stage I–III and stage X gastric cancer remained low between 1989 and 2008 (Figure 3a and b). For cardia cancer stage I–III and X, five-year survival remained about 20%, and for non-cardia cancer stage I–III and X, five-year survival remained about 31%. For stage IV cardia cancer, five-year survival was 1.0%, for non-cardia cancer, this was 1.9%. Changes in survival estimates between analyzed periods of diagnosis were not statistically significant.

Discussion

In the Netherlands, survival of gastric cancer remains dismal and has not improved during the past two decades as a result of differential epidemiological and clinical changes. The incidence of gastric cancer has markedly declined during the last century [1], mainly due to a fall in incidence of non-cardia cancer, which is confirmed in the present study. The incidence of cardia cancer increased in this study in the early 1990s, but since then it has been declining. The decline in incidence of non-cardia cancer was however steeper compared to cardia cancer. This results in a somewhat higher proportional incidence of cardia cancer nowadays in both genders. Some studies report an increase in cardia cancer [3,5], although others report a stable or declining incidence [2,4]. However, in several if not most studies the exact tumor location was often unspecified, thereby potentially biasing the results. In the current study, the distinction between cardia and non-cardia cancer was based on the International Classification of Disease classification system, which does not incorporate the nowadays frequently used Siewert classification. Although the classification in the registry's topography rules have not changed, changes in diagnostic procedures and definitions could have caused a shift from cardia cancer to distal esophageal cancer. Previous studies conducted in the Netherlands showed a marked rise in incidence of

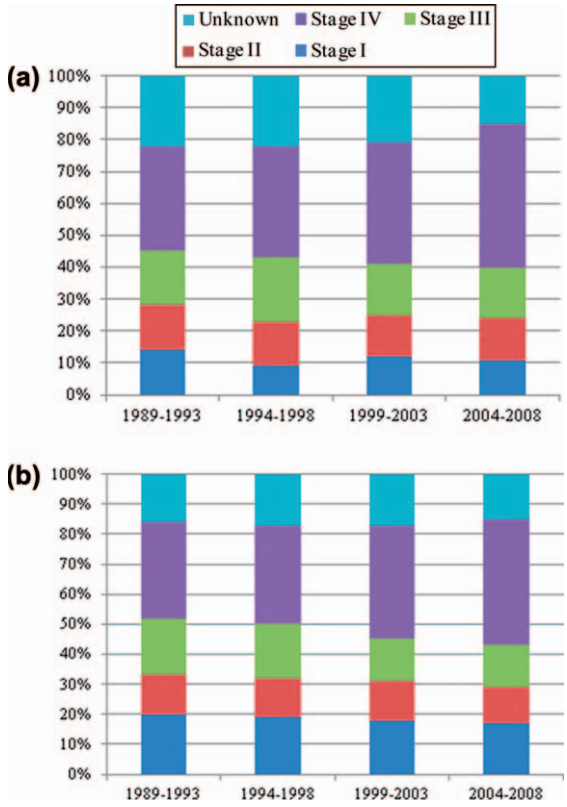

Figure 2. (a) Stage distribution according to period, cardia. (b) Stage distribution according to period, non-cardia.

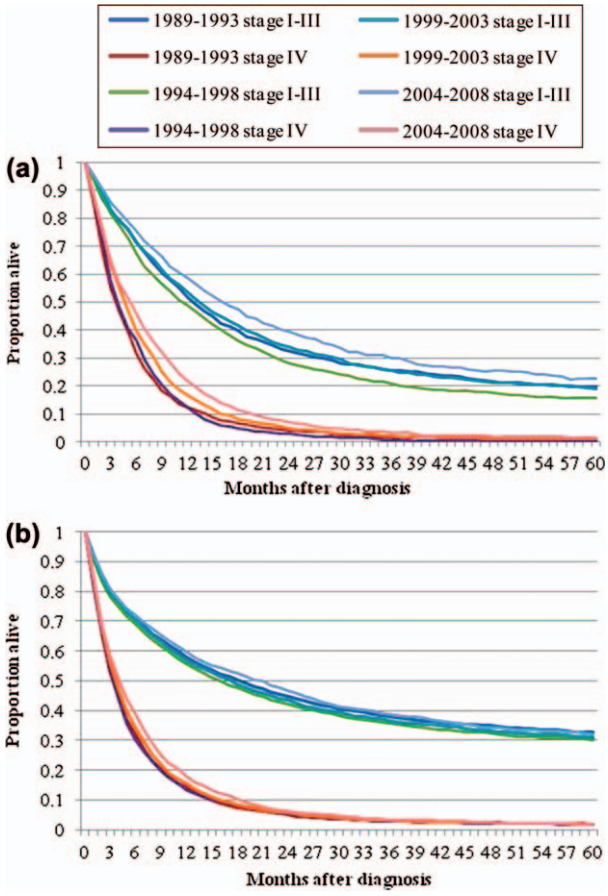

Figure 3. (a) Relative survival according to period, cardia. (b) Relative survival according to period, non-cardia.

distal esophageal cancer [4,6]. Although reclassification might partly explain the increase in esophageal adenocarcinoma, it is likely that the greater part of the increase in esophageal adenocarcinoma is a true rise in disease burden. Finally, in the 7th TNM classification, a tumor arising in the proximal 5 cm of the stomach and crossing the gastro-esophageal junction is classified as esophageal carcinoma. This could further influence the change in the incidence of esophageal and cardia cancer in the future.

Several factors are thought to affect the incidence of gastric cancer. *Helicobacter pylori* infection leads to chronic gastritis, which may progress to atrophic gastritis, intestinal metaplasia and loss of acid secretion. Eventually dysplasia and gastric cancer develop, especially in the distal stomach [14–16]. Eradication of *H. pylori* in patients with early gastric cancer substantially decreased the risk of development of metachronous gastric cancer, which suggests that eradication therapy has played a role in the decline in gastric cancer incidence [17]. Due to changes in lifestyle (i.e. improved hygiene and sanitation) and dietary pattern the prevalence of *H. pylori* infection has declined. Also, increased consumption of fruit and vegetables and lower salt consumption have reduced the risk of gastric cancer [18]. Cardia cancer differs from non-cardia cancer, biologically and epidemiologically. Two distinct etiologies have been described for cardia cancer. The first is associated with an *H. pylori* infection, suggesting a similar pathway as for non-cardia cancer [16,19]. The second etiology is associated with a high BMI and gastro-esophageal reflux disease which are independent risk factors for cardia cancer. A decreasing prevalence of *H. pylori* in combination with increasing prevalence of obesity in the Netherlands may explain the stabilization of cardia cancer incidence in our study during recent years.

For both types of gastric cancer, a rise in proportional incidence of stage IV cancer at the time of diagnosis was observed in the present study. Due to late presentation of symptoms and lack of pathognomonic signs gastric cancer is more likely to be detected in a late stage. The rise in stage IV cancer in our study might be due to stage migration; because of improved imaging modalities such as computed tomography distant metastases are seen at an earlier stage so more patients are classified in a more advanced stage group compared with earlier years when imaging techniques were less sensitive. In the studied period, three editions of the TNM classification were used in staging gastric cancer. In each consecutive classification stage IV disease was applied to a 'lower' T and N stage, which could have led to a higher proportion of patients with stage IV disease in this study. In countries where gastric cancer is endemic, such as Japan, screening programs have been developed [20], and gastric cancer is detected in a much earlier stage. In the Netherlands, this would not be cost-effective due to the much lower incidence rates. Besides differences in race, age, sex distribution and histological distribution, differences in staging (leading to stage migration) and treatment may be of influence on the survival discrepancy between East and West.

Over the study period, the prognosis of gastric cancer in the Netherlands remained dismal both for cardia and for non-cardia cancer. The prognosis for cardia cancer was worse compared to non-cardia cancer, which can largely be explained by different histopathological characteristics. Cardia cancer is mostly detected in a more advanced stage, with a deeper penetration of the stomach wall and more tumor positive lymph nodes. Furthermore, it is more often poorly differentiated and has a larger diameter [21,22]. In a study analyzing all types of gastric cancer, the presence of cardia cancer was an independent risk factor for lower survival, indicating this might be a more aggressive form of gastric cancer

[21]. As it is not cost-effective to perform a screening program for early detection of gastric cancer in a low incidence population, it is imperative to improve treatment to increase survival. Centralization may be part of a solution. Although a recent Dutch study showed no benefit of gastric cancer surgery in high volume versus low volume hospitals, due to a low percentage of high volume surgery, it has shown its benefit in esophageal cancer and cancer of the proximal gastric cardia [23,24]. Centralization for gastric cancer has been implemented since 2012. Improvement of the surgical and pathological technique as well as improvement of perioperative care is essential to improve survival.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Notice of correction

The version of this article published online ahead of print on 8th of Jul, 2013 contained an error on page 1. The author name "Michel J.W.M. Wouters" should have read "Michel W.J.M. Wouters". The error has been corrected for this version.