PART III

Surgical quality assurance

CHAPTER 11

Increased incidence and survival for esophageal cancer but not for gastric cardia cancer in the Netherlands

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ABSTRACT

BACKGROUND

A worldwide increasing incidence is seen for esophageal adenocarcinoma, but not for esophageal squamous cell carcinoma (SCC) and gastric cardia adenocarcinoma. Purposes of the current study were to evaluate the changing incidence rates of esophageal and gastric cardia cancer, and to assess survival trends.

PATIENTS AND METHODS

Patients diagnosed with esophageal adenocarcinoma (N = 12,195) or SCC (N = 9,046), or gastric cardia adenocarcinoma (N = 9,900) between 1989 and 2008 in the Netherlands were included. Changes in European Standard Population (ESP) and relative survival over time were evaluated.

RESULTS

Incidence rates for esophageal adenocarcinoma increased in males (+7.5%, $P < 0.001$) and females (+5.2%, $P < 0.001$), while the incidence for esophageal SCC remained stable in males (-0.2%, $P = 0.6$) and slightly increased in females (+1.7%, $P = 0.001$). The incidence for gastric cardia cancer decreased in males (-1.2%, $P < 0.006$), and remained stable in females (-0.2%, $P = 0.7$). Five-year survival for both M0 and M1 esophageal carcinoma doubled over the last 20 years. No significant changes in survival were found for M0 and M1 gastric cardia carcinoma.

CONCLUSIONS

In the Netherlands, a rising incidence is seen for esophageal adenocarcinoma, but not for gastric cardia adenocarcinoma. This finding most likely reflects true changes in disease burden, rather than being the result of changes in diagnosis or classification. The increased survival for esophageal carcinoma can be attributed to centralization of surgery, and an increased use of multimodality therapy, factors hardly acknowledged for gastric cancer.

INTRODUCTION

Esophageal and gastric cancer are, respectively, the sixth and second causes of cancer death worldwide, with an estimated 500,000 new cases of esophageal cancer and one million new cases of gastric cancer each year.[1]

Esophageal cancer is primarily composed of two histological types, adenocarcinoma and squamous cell carcinoma (SCC), each with a distinct etiology and specific risk factors.[2] Subtypes of gastric cancer are often based on topology, distinguishing cardia and non-cardia gastric cancer. Most gastric cancers are adenocarcinomas.

Worldwide, there has been a marked increase in the incidence of esophageal cancer over the last decades, which is mainly attributed to an increase in the incidence of adenocarcinoma of the esophagus in North America,[3,4] Europe[5] and Japan.[6] The incidence of SCC of the esophagus has remained stable or is declining.[3,5] For gastric cardia cancer, two studies have reported a rising incidence in the United States in the seventies and eighties, while the incidence since then has stabilized.[4,7] In the Netherlands, a rising incidence of adenocarcinoma of the esophagus has been reported as well from 1989 to 2003, while the incidence of esophageal SCC hardly increased, and gastric cardia cancer incidence rates were declining.[8,9] However, these data did not include a comprehensive analysis of incidence and survival for esophageal adenocarcinoma, esophageal SCC, and gastric cardia adenocarcinoma.

The first purpose of the current study was to give an update on incidence rates and stage distribution for esophageal adenocarcinoma and SCC, and gastric cardia adenocarcinoma in the Netherlands from 1989 to 2008. The second purpose was to evaluate survival patterns for these cancers during the same period.

PATIENTS AND METHODS

NETHERLANDS CANCER REGISTRY

Data were obtained from the Netherlands Cancer Registry (NCR), in which data is collected on all newly diagnosed malignancies in the Netherlands, a country of 16.7 million inhabitants. The NCR receives data from eight regional cancer registries, covering all hospitals in the Netherlands. Information on patient and tumor characteristics and treatment is routinely collected by trained registrars who extract this information from the hospital records 6-18 months after diagnosis. Topography and morphology are coded according to the International Classification of Diseases for Oncology (ICD-O)[10], based on information from the medical files, including the pathology report. Tumors are staged according to the International Union Against Cancer (UICC) TNM classification. Until December 1996, the UICC 4th edition was used,[11] from 1997 until 2001 the UICC 5th edition was used,[12] and as of January 2002, all tumors were coded according to the UICC 6th edition.[13] For esophageal carcinoma, the 4th, 5th, and 6th UICC TNM classifications were not different, except for a minor modification in the 5th edition with the introduction of the M1a and M1b classification. For gastric cardia cancer, 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. Vital status in the NCR is extracted from the medical records or is obtained by record linkage with the Dutch Central Bureau of Statistics, which registers all deceased persons in the Netherlands. As the NCR does not capture the cause of death, mortality rates were extracted from the Dutch Central Bureau of Statistics, separately for esophageal and gastric cancer. The study was approved by the NCR Review Board.

PATIENTS

Between January 1989 and December 2008, 22,530 cases of primary invasive esophageal (C15.0-15.9) and 9,963 cases of primary invasive gastric cardia cancer (C16.0) were diagnosed in the Netherlands. For the current study, adenocarcinomas (ICD-O morphology codes 8140-8142, 8144, 8145, 8190, 8200, 8210, 8211, 8230, 8255, 8260-8263, 8310, 8130, 8180, 8481, 8490, 8510, 8560, 8570, 8573-8576) of the esophagus or gastric cardia, and SCCs (ICD-O morphology codes 8051, 8052, 8070- 8076, 8078) of the esophagus were selected. Tumors with other or unknown histology (including 'No Otherwise Specified') of the esophagus (N = 1289) or gastric cardia (N = 63) were excluded, leaving 21,241 patients with esophageal cancer, and 9,900 patients with cardia cancer for analysis.

STATISTICAL ANALYSIS

Separate analyses were performed for esophageal adenocarcinoma (C15.0-15.9), esophageal SCC (C15.0-C15.9), and gastric cardia adenocarcinoma (C16.0). To evaluate trends over time, the study period was divided in four intervals of five years.

Incidence rates were calculated as the number of new patients per 100,000 inhabitants per year, and are age-standardized using the European Standardized Population (ESP).[14] The ESP reflects the incidence as if the population of the Netherlands would have the same age-composition as a hypothetical European population. Changes in incidence were evaluated with the estimated annual percentage change (EAPC), fitting a regression line to the natural logarithm of the rates using calendar year as a regressor variable.[15]

Differences in stage distribution between the various time-periods were calculated with a chi-square test. Stage IV gastric cardia adenocarcinoma comprises not only M1 disease but also locally advanced (T4N1-3, T1-3N3) M0 disease.[13] Therefore, stage IV-M0 and stage IV-M1 gastric cardia adenocarcinomas were analyzed separately.

Follow-up was complete until December 31st, 2009. Survival was calculated from the date of diagnosis until death of any cause (event) or alive at last follow-up (censored) by using the life-table method. Then, relative survival was calculated correcting for age- and gender-specific background mortality.[16] Mortality rates were obtained directly from the Dutch Central Bureau of Statistics as the absolute number of deaths per 100.000. All analyses were performed with SAS statistical software (version 9.2).

Table 1. Patient and tumor characteristics (N = 31,141)

	Esophageal adenocarcinoma (C15.0-15.9)		Esophageal SCC (C15.0-15.9)		Gastric cardia adenocarcinoma (C16.0)	
	N	%	N	%	N	%
Total	12195	*100.0*	9046	*100.0*	9900	*100.0*
Sex						
male	9566	*78.4*	5429	*60.0*	7640	*77.2*
female	2629	*21.6*	3617	*40.0*	2260	*22.8*
Age at diagnosis						
<60	2952	*24.2*	2661	*29.4*	2452	*24.8*
60-74	5124	*42.0*	4062	*44.9*	4380	*44.2*
≥75	4119	*33.8*	2323	*25.7*	3068	*40.0*
Tumor location						
cervical esophagus	52	*0.4*	400	*4.4*		
intrathoracic upper 1/3	182	*1.5*	1106	*12.2*		
intrathoracic middle 1/3	1003	*8.2*	3148	*34.8*		
intrathoracic lower 1/3	10211	*83.7*	3509	*38.8*		
other/unknown	747	*6.1*	883	*9.8*		
gastric cardia					9900	*100.0*
Tumor grade						
well/moderate	3706	*30.4*	3651	*40.4*	3047	*30.8*
intermediate/poor	4669	*38.3*	2790	*30.8*	4465	*45.1*
unknown	3820	*31.3*	2605	*28.8*	2388	*24.1*

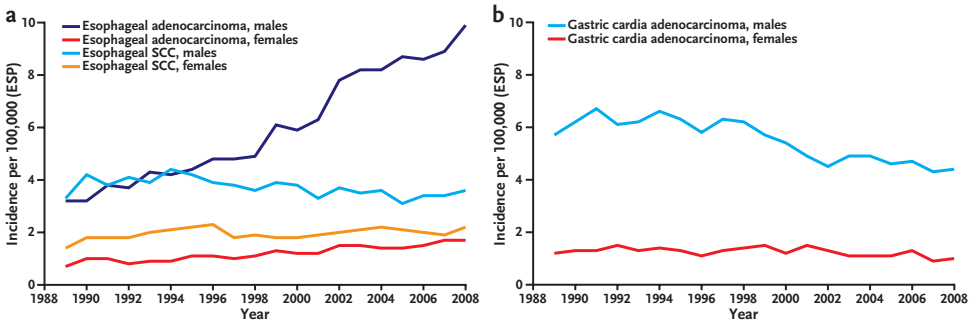
SCC: Squamous Cell Carcinoma

RESULTS

Between January 1st, 1989 and December 31st, 2008, 12,195 patients with esophageal adenocarcinoma, 9,046 patients with esophageal SCC, and 9,900 patients with gastric cardia adenocarcinoma were diagnosed in the Netherlands. Patient and tumor characteristics are summarized in Table 1. The number of males exceeded the number of females in all three subgroups. Median age at diagnosis was 69.6 years for esophageal adenocarcinoma, 66.9 years for esophageal SCC and 69.3 years for gastric cardia adenocarcinoma. The majority (83.7%) of esophageal adenocarcinomas were located in the lower esophagus. Esophageal SCC was more evenly distributed throughout the esophagus.

The incidence of esophageal adenocarcinoma increased in males in the period 1989-2008 (Figure 1a): the ESP increased from 3.2 per 100,000 inhabitants per year in 1989 to 9.9 in 2008 with an estimated annual percentage change (EAPC) of +7.5 (95% CI +6.8 to +8.2, $P < 0.001$). In females, the ESP of esophageal adenocarcinoma also increased, but to a lesser extent: from 0.7 in 1989 to 1.7 in 2008, with an EAPC of +5.2 (95% CI +4.2 to +6.2, $P < 0.001$). For esophageal SCC, no significant change was detected in males (EAPC -0.2, 95% CI -1.0 to 0.6, $P = 0.6$), while in females the incidence slightly increased (EAPC +1.7, 95% CI +0.8 to +2.7, $P = 0.001$). The incidence of gastric cardia carcinoma decreased over the years in males but did not significantly change in females (Figure 1b): in males, the ESP decreased from 5.7 in 1989 to 4.4 in 2008, with

Figure 1. Incidence of (a) esophageal carcinoma and (b) gastric cardia adenocarcinoma in the Netherlands, 1989-2008



ESP: European standardized population
SCC: squamous cell carcinoma

an EAPC of -1.2 (95% CI -2.0 to -0.4, $P = 0.006$), and in females, the ESP decreased from 1.2 in 1989 to 1.0 in 2008, with an EAPC of -0.2 (95% CI -0.9 to 1.2, $P = 0.7$).

Differences in stage distribution were noted (all $P < 0.001$), but in all three tumor types about 40% of all tumors were diagnosed in a non-metastatic stage. The other 60% of tumors were either staged as M1 disease, or did not have a stage group assigned. Changes in stage distributions over the years for esophageal adenocarcinoma and SCC showed a similar pattern over time (Figures 2a and 2b). The percentage of patients with an unknown stage steadily decreased, with a corresponding increase in the proportion of stage IV patients. Comparing changes in tumor location for esophageal adenocarcinoma versus SCC, there was a relative increase in distally located tumors for adenocarcinoma (77.2% - 87.7%), without major changes in the distribution of SCCs (Figures 3a and 3b). For gastric cardia adenocarcinoma (Figure 2c), the proportion of patients with no stage assigned also decreased, but this was less prominent (from 19.8% to 15.0%). With the incorporation of the absolute number of metastatic lymph nodes into the TNM classification as of 1997, differences in stage distribution for gastric tumors might very well reflect a staging difference rather than a true shift in stage distribution.

Mortality rates per 100.000 inhabitants in the Netherlands increased for esophageal carcinoma, both for males (from 6.8 to 13.9) and females (3.1 to 5.1). Mortality rates for gastric cancer decreased for males (18.6 to 10.7) and females (11.5 to 6.6). Survival estimates for esophageal and gastric cardia carcinoma are shown in Table 2. Five-year relative survival significantly increased from 12.2% to 25.3% for M0 esophageal adenocarcinoma and from 11.6% to 18.9% for M0 esophageal SCC. No significant increase in survival was detected for M0 gastric cardia carcinoma (19.0% to 20.6%). In the metastatic setting, 2-year relative survival significantly increased for esophageal carcinoma, but not for gastric cardia carcinoma. Survival curves are depicted in Figure 4.

Figure 2. Stage distribution of (a) esophageal adenocarcinoma, (b) esophageal squamous cell carcinoma, and (c) gastric cardia adenocarcinoma in the Netherlands, 1989-2008

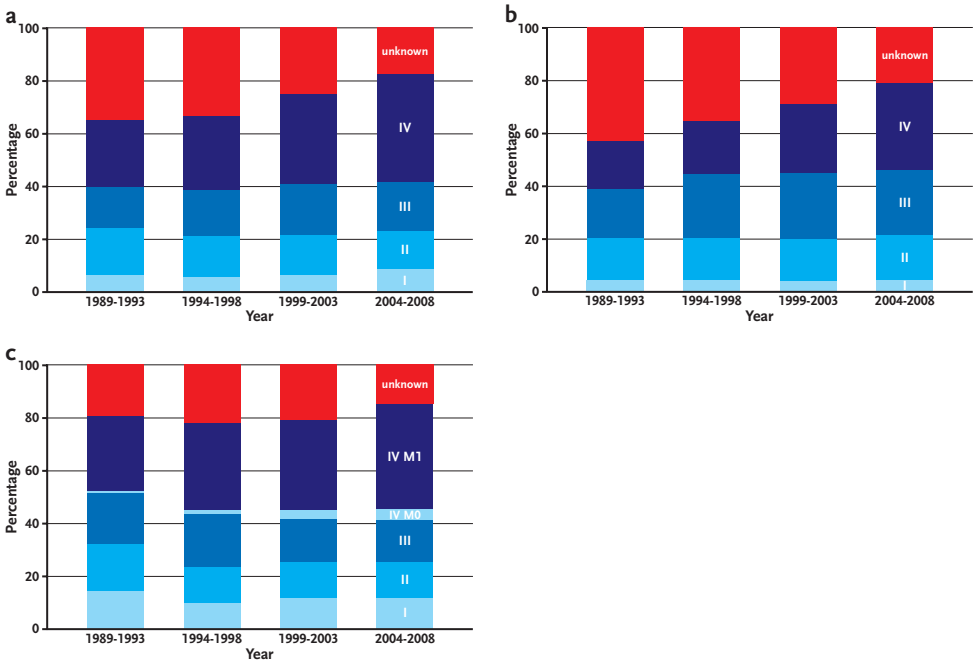
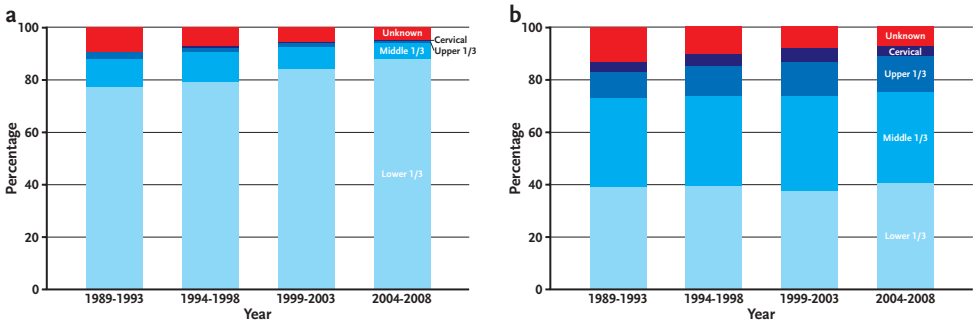


Figure 3. Relative distribution of location for (a) esophageal adenocarcinoma and (b) esophageal squamous cell carcinoma



DISCUSSION

Worldwide, the incidence of esophageal cancer is increasing. In the United States, the incidence of esophageal cancer has shown a six-fold rise over the last three decades.[4] This is entirely caused by a rise in the incidence of esophageal adenocarcinoma, primarily in white males.[3] In Europe, mainly the Northern part, there has also been an increase in the incidence of esophageal adenocarcinoma in men, but not in women.[5] The incidence of SCC has remained stable in Europe and the United States.[3,5] In the current study, similar

patterns were found. The incidence of esophageal adenocarcinoma in males showed a three-fold increase over two decades (1989-2008), with a smaller increase in females. For SCC, the incidence remained constant in males, and slightly increased in females, who increased their smoking habits over the past decades.

For gastric adenocarcinoma, there has been a worldwide decrease in the incidence of non-cardia gastric cancer over the past decades.[17,18] For gastric cardia cancer, early studies report an increasing incidence in the West Midlands (England),[19] Connecticut (US),[20] and the SEER regions (US),[21] but none of these studies report data after 1989. More recent studies from the United States,[4,7] Sweden,[22] and Spain[23] confirmed this increase until the early nineties, after which the incidence for gastric cardia cancer reached a plateau followed by a slow decrease as of the late nineties. Other studies, including the current study, report a stable or decreasing incidence of gastric cardia cancer over the last decades.[24,25] Therefore, the often cited[17,26,27] increasing incidence of cardia gastric cancer in developed countries should be considered carefully, and be judged in the light of more recent observations.

In the current study, incidence rates significantly changed over time for adenocarcinoma of the esophagus in both males and females, for SCC in females, and for gastric cardia carcinoma in males. Time trends in disease incidence should be interpreted cautiously, because they might reflect changes in diagnostics or reclassification of tumors, rather than representing a true change in disease burden. With the refinement of various diagnostic modalities in general, and the increased use of endoscopy in patients with reflux disease or Barret's esophagus, improved diagnosis might be a reason for the increased incidence of esophageal adenocarcinoma in the Netherlands. However, improved diagnosis would be present in all disease entities, in both sexes and throughout the entire esophagus in a comparable way. Furthermore, improved diagnosis would mainly lead to an increased incidence of early stage tumors, but this is not observed in the current study.

Another explanation for changes in incidence is reclassification. Because there are no clear morphologic differences that distinguish adenocarcinomas of the lower esophagus from those of the cardia, tumors of the gastro-esophageal junction are vulnerable to reclassification. And although the registry's topography classification rules have remained unchanged over the study period, clinical classification of tumors of the gastro-esophageal junction might have shifted towards esophageal cancer. However, the six-fold increase in the incidence of esophageal adenocarcinoma is not fully compensated by the decrease in gastric cardia adenocarcinomas. Furthermore, reclassification would be equally present in males and females. Therefore, 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.

Table 2. Five-year relative survival of non-metastatic (M0) and metastatic (M1) esophageal and cardia carcinoma in the Netherlands, 1989-2008

	Esophageal adenocarcinoma		Esophageal SCC		Cardia adenocarcinoma	
	%	95% CI	%	95% CI	%	95% CI
M0 disease						
1989-1993	12.2	10.0-14.6	11.6	9.9-13.6	19.0	16.7-21.3
1994-1998	14.9	13.0-16.9	11.9	10.3-13.6	15.5	13.7-17.4
1999-2003	17.4	15.8-19.2	13.3	11.7-15.1	18.4	16.4-20.5
2004-2008	25.3	22.9-27.8	18.9	16.5-21.5	20.6	17.7-23.8
M1 disease						
1989-1993	3.3	1.8-5.7	6.0	3.6-9.2	4.2	2.8-6.0
1994-1998	5.3	3.7-7.3	4.7	2.9-7.0	3.1	2.1-4.5
1999-2003	5.7	4.5-7.1	5.4	3.8-7.4	4.1	2.8-5.5
2004-2008	9.0	7.7-10.4	10.1	8.0-12.4	6.0	4.6-7.7

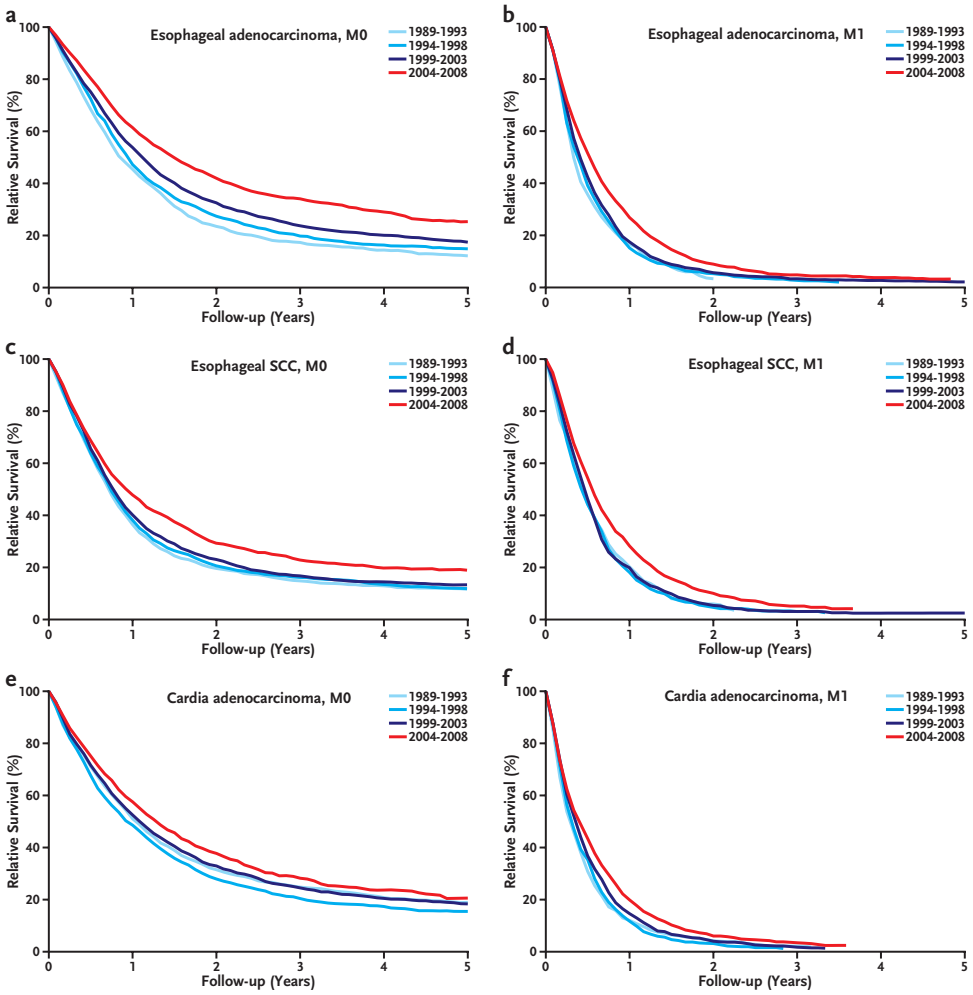
95% CI: 95% confidence interval, SCC: squamous cell carcinoma

All three studied cancers have their specific etiologic factors. Esophageal adenocarcinoma has been associated with obesity[28], smoking[21], reflux disease[29], Barrett's esophagus[30], high meat consumption[31], and a high fat consumption[31], whereas esophageal SCC has been associated with alcohol consumption[21], smoking[21], and low fruit intake[32]. For gastric cardia adenocarcinoma, risk factors are male sex and white race,[33] obesity[28], reflux disease[34], meat consumption[31], and fat consumption[31]. These risk factors show a significant overlap with the risk factors for esophageal adenocarcinoma, making it difficult to explain why incidence changes for esophageal and gastric cardia adenocarcinoma are discordant. It has been suggested that these tumors consist of two different histopathological entities but evidence for this is limited[35].

Others have favored the hypothesis that gastric cardia cancer consists of two distinct etiologies: one arising from *H. pylori* associated severe atrophic gastritis and being of intestinal or diffuse subtype similar to non-cardia cancer, and one related to reflux disease and intestinal in subtype, similar to esophageal adenocarcinoma.[34] With a decreasing incidence of *H.* pylori, the first subtype might be responsible for the decreasing incidence of cardia carcinoma.[9] Although this might be a plausible explanation, underlying mechanisms for the differences in incidence trends need further investigation before definite conclusions can be drawn.

For both M0 and M1 esophageal cancer, relative survival rates improved during the study period. For M0 tumors, this may be the result of centralization of esophageal cancer surgery in the Netherlands. Centralization improves patient selection, perioperative care, surgical experience, and decreases failure to rescue in case of complications. As of 2006, a yearly minimum of ten esophagectomies per hospital was enforced by the Dutch Health Care Inspectorate. In two regions of the Netherlands, the minimum volume was introduced earlier, significantly improving survival.[36] Secondly, the increased

Figure 4. Relative survival of patients with esophageal and gastric cardia carcinoma in the Netherlands, 1989-2008. Relative survival estimates and confidence intervals are shown in Table 2



use of neoadjuvant chemotherapy or chemoradiation might have contributed to the better survival rates for M0 esophageal cancer.[37,38] From 2004 to 2008, a large Dutch multicenter trial has explored the use of preoperative chemoradiation in esophageal cancer.[39] All patients in this trial were included in the current analysis. For M1 tumors, the increase in survival can be attributed to stage migration due to improved detection of distant metastases.

A very recent study shows that esophagectomies were centralized to a great extent over the past 20 years in the Netherlands, while most gastrectomies are performed in low volume centers. High volume esophagectomies were associated with lower postoperative mortality, while there were hardly any high volume gastrectomies to conduct a properly

powered volume-outcome analysis for gastrectomy.[40] Furthermore, in the study period multimodality therapy has been administered more frequently in esophageal as compared to cardia carcinoma (results not shown). This might explain why for gastric cardia cancer, relative survival did not significantly increase, corresponding with earlier results from one region in the Netherlands.[41] Because postoperative chemoradiotherapy and perioperative chemotherapy have emerged as adjuvant strategies that improve outcome in gastric cancer, it is expected that survival will increase over the coming decades.

In conclusion, the current manuscript reveals an increase in the incidence of esophageal adenocarcinoma both in males and females, and a decrease in the incidence of gastric cardia adenocarcinoma in males. These are most likely true changes in disease burden, rather than being caused by either improved diagnosis or reclassification. The question why incidence trends for esophageal and cardia adenocarcinoma are different remains to be elucidated, but the existence of two different types of gastric cardia cancer is a possible explanation.

The improved survival for M0 esophageal carcinoma reflects an increasing number of esophagectomies performed in high-volume centers and the increased use of modern multi-modality therapy. These two factors are poorly acknowledged in treating gastric cancer in the Netherlands, which might explain why no significant increase in survival was detected in this tumor type.

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