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Trend breaks in incidence of non-cardia gastric cancer in the Netherlands

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ABSTRACT

Introduction: The incidence of gastric cancer declined over the past decades. Recently, unfavorable trend breaks (i.e. rise in incidence) were seen for non-cardia cancer in younger age groups in the US. It is unclear whether these also occur in other Western countries. We aimed to analyze the gastric cancer incidence trends by age, sex, subsite and stage in the Netherlands.
Methods: Data on all patients with gastric adenocarcinoma diagnosed from 1973 to 2011 ($n = 9093$) were obtained from the population-based Eindhoven cancer registry. Incidence time trends (European standardized rates per 100,000) were separately analyzed by sex, age group (<60, 60–74, and >75 years), subsite, and pathological stage. Joinpoint analyses were performed to discern trend breaks, age–period–cohort analyses to examine the influence of longitudinal and cross-sectional changes.
Results: The incidence of non-cardia cancer declined annually by 3.5% (95% CI −3.8; −3.3). However, in males <60 years, the incidence flattened since 2006, and tended to rise in those >74 years. This pertained to corpus cancers. The incidence of cardia cancer peaked in 1985 and decreased subsequently by 2.4% (95% CI −3.2; −1.5) yearly. The absolute incidence of stage IV disease at first diagnosis initially decreased, but then remained stable over the past 15–20 years.
Conclusions: The incidence of non-cardia cancer declined over the past four decades in the Netherlands, but now seems to be stabilizing particularly in males. Unfavorable trend breaks are seen for corpus cancer in younger and older males. The trend breaks in the Netherlands are however not similar to those observed in the US.

1. Introduction

Gastric cancer remains the second leading cause of death from cancer worldwide, although the incidence has steadily declined over the past sixty years [1–3]. This may reflect the simultaneous cohort-specific decrease in *Helicobacter pylori* acquisition, its most important carcinogen [4]. Consequently, a further decline in gastric cancer incidence in young persons would be expected.

Recent incidence trend studies, however, reveal an unfavorable trend break. The incidence of non-cardia gastric cancers in younger age groups (<50 years) has stabilized or even started to rise again in the United States since 1977 [5,6]. Furthermore, the incidence of cardia cancer has increased over the past decades in Asia [5,7,8]. The cause and extent of these discrepant trends are unknown.

We therefore aimed to closely analyze the gastric cancer incidence trends by age, sex, subsite and stage in the Netherlands, to find out whether the observed trends in the US are taking place in Western European countries as well. Detailed trend studies provide essential information for the understanding of recent patterns and are necessary to anticipate future trends and guide etiological investigations.

2. Methods

2.1. Study population

For our analyses we used data from the Eindhoven Cancer Registry, which has prospectively collected data on all patients with newly diagnosed cancer in the southern part of the Netherlands since 1955 [9]. Until 1988, the registry area covered 1.0 million inhabitants. In both 1988 and 2001 the region has been expanded and covers nowadays a population of 2.4 million

Abbreviations: APC, annual percentage change; CI, confidence interval; ESR, European standardized rates; ICD-O, International Classification of Diseases for Oncology; NOS, not otherwise specified.

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inhabitants (~15% of the Dutch population). The area offers good access to specialized medical care in 10 general public hospitals and is served by 6 regional pathology laboratories. Trained registry personnel actively collect data on diagnosis, stage, treatment and survival from the medical records after notification by pathologists and medical registration offices. Tumors were registered according to the ICD-O (International Classification of Diseases for Oncology) edition of the respective period [10].

In this study, we included all patients newly diagnosed with gastric cancer between 1973 and 2011. Only adenocarcinomas were included (morphology codes 8010, 8012, 8020, 8021, 8140, 8141, 8142, 8143, 8144, 8145, 8200, 8201, 8210, 8211, 8221, 8230, 8255, 8260, 8261, 8263, 8310, 8440, 8453, 8470, 8480, 8481, 8490, 8500, 8512, 8560, 8570, 8574, 8890). This included 95% of the total number of gastric carcinomas. We defined the following subsite categories: (1) cardia, (2) fundus, (3) corpus (including lesser and greater curvature), (4) antrum, (5) pylorus, (6) overlapping sites, and (7) unspecified subsite (NOS). Because of changing coding rules, incidence rates of the subsites are shown from 1985 to 2011.

Stage at diagnosis was primarily based on the pathologists' report, using the TNM classification according to the edition of the respective period [11], or when missing, complemented by the clinical stage. Incidence rates are shown from 1975 to 2011, because stage was included in the registry from 1975.

2.2. Statistics

Incidence rates were calculated for the period 1973–2011. Age-adjustment was performed by direct standardization according to the European standard population (European standardized rates [ESR], per 100,000 person years). Results are presented as 3-year moving averages (for 1973 and 2011 as 2-year moving averages). Incidence rates were calculated by subsite, sex, age group (<60, 60–74 and 75 and older), and stage.

Temporal changes in incidence rate were evaluated by calculating the annual percentage change (APC) and the corresponding 95% confidence interval (CI) using Joinpoint software. Joinpoint is statistical software for the analysis of trends using Joinpoint models, that is models where several different lines are connected together at the "joinpoints". 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 = calendar year; then $\text{APC} = 100 \times (e^{a} - 1)$). Joinpoint regression analyses were performed to discern significant changes in the trend which we defined as trend breaks, and, if present, when they occurred [12]. In case a trend break was observed after a period of decreasing incidence, we defined this as an unfavorable trend break as the incidence then started to flatten or even increase.

Age–period–cohort analyses were performed to jointly examine the influence of longitudinal and cross-sectional changes [13,14]. Patients aged younger than 20 (0.01% of all cases) and 90 or older (1%) were excluded from these analyses because of the small number of cases in these groups. The population was divided into 5-year age groups (i.e. 20–24, ..., 85–89), 5-year calendar periods (except the first and last period: 1973–1980, 1981–1985, ..., 2001–2005, 2006–2011) and matching 10-year birth cohorts (except the first and last cohorts due to longer periods of diagnosis: e.g. the oldest group in the first period (1973–1980) was born 1883–1895, ..., youngest group in last period (2006–2011) was born 1981–1991). The GENMOD procedure of the SAS package was used to fit a series of Poisson regression models, to estimate the separate effects of age, time of diagnosis and birth cohort on the trend in incidence, according to the models described by Clayton and Schifflers [13,14]. To test the goodness-of-fit of the models with the observed incidence rates and to test the models against one another, deviances and differences between the deviances with appropriate degrees of freedom were used. The following models were fitted: the age, age–drift, age–period, age–cohort, and age–period–cohort model. Drift is a linear component of the overall rate of change in the incidence rate with time that describes models for which the age–period and age–cohort parameters fit the data equally well. Such a model thus serves as an estimate of the rate of change of a regular trend [14]. Trends in incidence were evaluated according to gender and subsite (cardia versus non-cardia).

Analyses were performed using SAS 9.1 (SAS Institute, Cary, NC, U.S.A.). p-values were two-sided and values <0.05 were considered significant. The software for the joinpoint analyses was the Joinpoint Regression Program, version 3.5.4 of the National Cancer Institute.

3. Results

3.1. Overall trends

Between 1973 and 2011 a total of 9093 gastric adenocarcinoma cases were registered in the Eindhoven Cancer Registry

Table 1
Patient characteristics of stomach cancer patients (adenocarcinoma only) in the southern Netherlands according to period of diagnosis.

	1973–1980	1981–1985	1986–1990	1991–1995	1996–2000	2001–2005	2006–2011	Total	p-value X^2-test
Number of patients	1182	791	1258	1539	1406	1331	1586	9093	
% males	62	63	62	63	65	63	64	62	0.7
Age (%)									
<60 years	25	25	21	20	21	21	18	25	<.0001
60–74 years	47	44	43	44	46	44	40	47	
>75 years	28	31	36	36	34	36	41	28	
Subsite (%)									
Cardia	10	18	21	23	23	22	27	21	<.0001
Non-cardia									
Fundus	1	1	2	1	2	2	2	2	
Corpus, incl lesser and greater curvature	6	21	20	21	21	20	18	18	
Antrum	7	18	20	20	22	20	20	19	
Pylorus	5	7	6	6	6	7	6	6	
Overlapping lesion of stomach	15	22	26	25	22	23	21	22	
Not otherwise specified	57	13	5	3	4	7	6	12	
TNM stage distribution (%)[a]									
1	3	8	14	18	17	15	13	13	<.0001
2	11	21	12	14	15	14	11	14	
3	8	20	19	14	14	14	13	14	
4	38	41	32	32	31	39	44	37	
X	41	10	23	22	22	18	18	22	

[a]Primarily referring to pathological stage, supplemented with clinical stage in case pathological stage is missing.