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Gastric cancer trends in Estonia 1995–2014 by age, subsite, morphology and stage

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ABSTRACT

Background: Gastric cancer (GC) is among the most common cancers and one of the leading causes of cancer deaths globally. In general, the incidence of GC has declined and survival improved in Europe. Nevertheless, previous analysis has shown that survival of GC patients in Estonia is still significantly lower compared to some European countries. Therefore, to improve patient outcomes, better overview of GC epidemiology is needed. The aim of this study was to describe the incidence and survival of GC in Estonia 1995–2014 in relation to age, subsite, morphology, and the extent of disease.

Material and methods: We used data from the population-based Estonian Cancer Registry on all incident cases of GC diagnosed in 1995–2014. Incidence rates and relative survival were calculated. Joinpoint regression modeling was used to estimate annual percentage change for incidence trends. Data were analyzed by age, sex, subsite, morphology, and the extent of disease. Changes between 1995–1999 and 2010–2014 were assessed.

Results: The overall incidence of GC in Estonia decreased in 1995–2014. The age-standardized (world) incidence declined significantly for both sexes, for patients below 70 years of age, adenocarcinomas, NOS and other morphologies, non-cardia and unspecified cases, and for all known stages. Approximately 40% of GC cases were diagnosed with distant metastasis. Overall age-standardized 5-year relative survival of GC patients increased from 20% to 28%. Survival improved the most in age group 50–69 years. A large survival gain was also seen for localized (from 55% to 70%) and locally/regionally spread disease (from 23% to 37%).

Conclusions: In Estonia, the incidence of GC has declined and relative survival increased. However, special emphasis needs to be put on improving survival among men, elderly and in patients with metastatic disease.

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Introduction

Gastric cancer (GC) is among the most common cancers and one of the leading causes of cancer deaths globally [1]. In Europe, there were 107,000 deaths in 2012 due to GC [2]. Despite still being a frequent disease, some epidemiologic changes have occurred. During the last decades, the incidence of GC has decreased and the main reasons for this change are a decline in *Helicobacter pylori* infection and smoking, and better hygiene and availability of fresh food [3–5]. The biggest decrease in GC incidence has been seen in Southern and Western Europe, which has created a gap in disease incidence between Eastern and other parts of Europe [6]. Additionally, a steady decline in mortality of GC has been reported in Europe since 1980 [7] and survival of GC has improved in Europe, USA and Asian countries during the last decades [1, 7–9].

GC is a heterogeneous disease in many aspects. There is a clear gender difference, since the incidence of GC is higher in men than in women [2,8,10,11]. Also, women have significantly better relative survival compared to men [8,12]. In addition, the survival is lowest in older people, regardless of the extent of disease [8,13,14]. Significant differences in survival are also seen for distinct disease locations, as survival is higher in patients with non-cardia cancer than with cardia cancer [8]. In Europe, there are also geographical differences: the average 5-year relative survival in Eastern Europe is approximately 10 percentage units lower than in Southern and Central Europe [12]. These remarkable discrepancies in 5-year survival rates may be explained by differences in disease stage at diagnosis and accessibility to good care, differences in cancer biology, and variations in socioeconomic status, lifestyle, and general health between European populations [12].

According to CONCORD-3 study, the 5-year survival of GC has improved in Estonia from 22% in 2000–2004 to 29% in 2010–2014. The survival in 2010–2014 is similar to the survival in Northern European countries like Finland (26%), Sweden (25%), and Norway (27%). However, 5-year survival of Estonian GC patients is still significantly lower than in

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Table 1. Incidence cases of gastric cancer in Estonia 1995–2014.

Characteristics	Total *n*	%	1995–1999 *n*	%	2000–2004 *n*	%	2005–2009 *n*	%	2010–2014 *n*	%	*p*-value[a]
All cases	8744	*100*	2456	*100*	2167	*100*	2132	*100*	1989	*100*	
Microscopic verification	7896	*90*	2179	*89*	1930	*89*	1954	*92*	1833	*92*	<.001
Death certificate only	150	*2*	36	*2*	57	*3*	32	*2*	25	*1*	.55
Autopsy	151	*2*	41	*2*	35	*2*	44	*2*	31	*2*	.77
Age groups											
0–15	2	*0*	0	*0*	1	*0*	0	*0*	1	*0*	
15–49	777	*9*	244	*10*	210	*10*	190	*9*	133	*7*	<.001
50–69	3840	*44*	1196	*49*	993	*46*	887	*42*	764	*38*	<.001
70 +	4125	*47*	1016	*41*	963	*44*	1055	*49*	1091	*55*	<.001
Gender											
Men	4786	*55*	1354	*55*	1179	*54*	1157	*54*	1096	*55*	1.0
Female	3958	*45*	1102	*45*	988	*46*	975	*46*	893	*45*	
Subsite											
Cardia	666	*7*	146	*6*	179	*8*	162	*8*	179	*9*	<.001
Non-cardia	5648	*65*	1552	*63*	1298	*60*	1290	*60*	1508	*76*	<.001
Unspecified	2430	*28*	758	*31*	690	*32*	680	*32*	302	*15*	<.001
Morphology											
Adenocarcinoma	4271	*49*	1132	*46*	1022	*47*	1040	*49*	1077	*54*	<.001
Signet cell carcinoma	2365	*27*	674	*27*	571	*26*	624	*29*	496	*25*	.061
NOS	925	*11*	314	*13*	256	*12*	193	*9*	162	*8*	<.001
Other	1183	*13*	336	*14*	318	*15*	275	*13*	254	*13*	.35
Extent of disease											
Localized	2051	*24*	577	*23*	493	*23*	496	*23*	485	*24*	.485
Local/ regional spread	2077	*24*	612	*25*	505	*23*	504	*24*	456	*23*	.074
Distant metastasis	3522	*40*	1019	*42*	935	*43*	854	*40*	714	*36*	<.001
Unknown	1094	*12*	248	*10*	234	*11*	278	*13*	334	*17*	<.001

[a]Comparing periods 1995–1999 and 2010–2014.

Austria (35%), Belgium (38%), Germany (34%), USA (33%), and many Asian countries like Japan (60%) and China (36%) [9], showing that there may be some shortage in GC management in our country. To find ways to improve patient outcomes, a detailed analysis of GC survival is needed. Therefore, the aim of this population-based study was to describe the incidence and survival of GC in Estonia 1995–2014 in relation to age, sex, subsite, morphology, and extent of the disease.

Material and methods

The present study was carried out with permission of the Research Ethics Committee of the University of Tartu.

We used the data from the Estonian Cancer Registry (ECR), a population-based registry with nationwide coverage [15]. The ECR provided data on all cases of GC (ICD-10 code C16) diagnosed in Estonia in 1995–2014. The following quality indicators were calculated: percentage of microscopically verified cases, percentage of death certificate only cases, percentage of autopsy detected cases, and percentage of unknown extent of disease. Cases diagnosed at autopsy and cases based only on death certificate were excluded from survival analysis.

The patients were grouped according to the year of diagnosis (1995–1999; 2000–2004; 2005–2009; 2010–2014) and by age groups (15–49 years, 50–69 years and $\geq$70 years). According to morphology, cases were grouped as adenocarcinoma, signet cell carcinoma, NOS (not otherwise specified), and other. By subsite, the cases were grouped as cardia (C16.0), non-cardia (C16.1–C16.8), and unspecified (C16.9). The extent of disease was defined as localized, locally/regionally spread (including spread to neighboring tissues and/or regional lymph nodes), distant, and unknown.

Age-specific and age-standardized (world) GC incidence rates were modeled and the estimated annual percentage change (APC) or average annual percentage change (AAPC) with 95% confidence intervals (CI) were calculated with Joinpoint Regression Program (version 4.1.1.1) from the Surveillance Research Program of the US National Cancer Institute (http://surveillance.cancer.gov/joinpoint/).

For survival analysis, the patients were followed up for vital status until 31 December 2014, via linkage with the Estonian Population Registry. In case of death or emigration, the respective date was ascertained. 1-year and 5-year relative survival ratios (RSR) were calculated as the ratio of the observed survival of cancer patients and the expected survival of the underlying general population. The latter was calculated according to the Ederer II method using national life tables for Estonian population stratified by age, gender and calendar year [16]. For 2010–2014, period analysis was used to calculate survival [17].

The statistical significance of the difference between proportions was tested using a Chi-square test. The International Cancer Survival Standard (ICSS) population was used for age-standardizing survival estimates [18]. Stata 14 software (StataCorp LP, TX, USA) was used for all analyses; the *strs* module was used for survival analysis [19].

Results

Incidence

In total, 8744 cases of GC were diagnosed in Estonia in 1995–2014 (Table 1). The average annual number of cases decreased from 436 in 1995–1999 to 397 in 2010–2014. The proportion of microscopically verified cases increased significantly during the study period from 89% to 92%. The

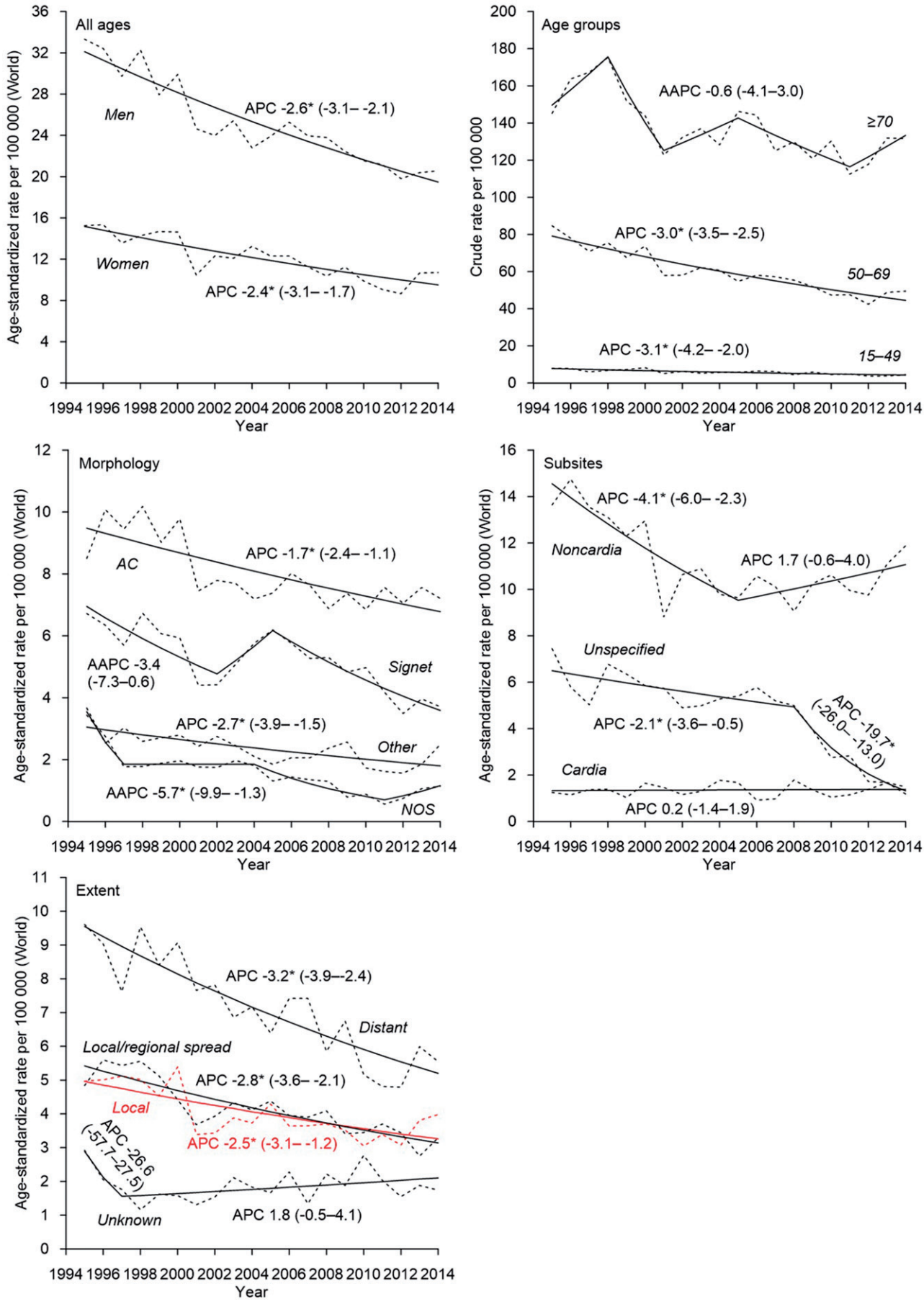

Figure 1. Observed (dashed line) and modeled (solid line) age-standardized (world) annual percentage change (APC) and average annual percentage change (AAPC) with 95% confidence intervals for trends in gastric cancer incidence in Estonia, 1995–2014. (*)The APC is significantly different from zero at alpha = 0.05.

Table 2. One- and five-year relative survival ratios (RSR) for stomach cancer in Estonia, 1995–2014.

	1995–1999				2000–2004				2005–2009				2010–2014[a]			
	1-y RSR	95% CI	5-y RSR	95% CI	1-y RSR	95% CI	5-y RSR	95% CI	1-y RSR	95% CI	5-y RSR	95% CI	1-y RSR	95% CI	5-y RSR	95% CI
Total	39	37–41	20	19–22	42	40–44	22	20–24	45	42–47	24	22–27	**46**	**43–48**	**26**	**24–29**
Total (age-standardized)	38	36–40	20	18–22	42	40–44	22	20–24	45	43–47	25	22–27	**48**	**45–50**	**28**	**25–30**
Sex (age-standardized)																
Male	35	33–38	19	16–22	41	38–44	21	18–24	45	42–48	24	21–27	**45**	**42–48**	**25**	**22–28**
Female	42	39–45	22	20–25	43	40–46	24	21–27	46	42–49	26	23–29	**51**	**47–54**	**32**	**28–36**
Age at diagnosis																
15–49	52	46–59	31	25–37	56	49–63	25	20–32	49	42–56	28	22–35	62	53–70	36	28–43
50–69	41	39–44	21	19–24	46	43–49	24	21–27	49	46–52	27	23–30	**55**	**51–58**	**31**	**27–34**
70+	32	29–35	16	14–19	34	31–38	20	17–23	40	37–43	22	19–25	37	33–40	22	19–25
Subsite																
Cardia	36	28–44	18	11–25	40	33–48	17	11–23	49	41–57	19	13–27	48	40–55	22	15–29
Non-cardia	44	42–47	25	22–27	47	44–50	27	24–30	48	45–50	27	25–30	48	46–51	29	26–32
Unspecified	27	23–30	11	9–14	32	28–35	15	12–18	38	34–41	20	17–24	31	26–37	18	14–22
Morphology																
Adenocarcinoma	46	43–49	26	23–29	46	43–50	28	25–31	49	46–52	26	23–29	51	48–54	30	26–33
Signet cell carcinoma	41	37–45	20	17–24	48	43–52	21	17–24	46	42–50	24	20–28	45	41–50	23	19–27
NOS	14	10–18	5	2–8	14	9–19	5	2–9	14	9–20	8	4–14	7	4–11	3	1–6
Other	28	23–33	14	10–18	34	29–40	18	14–23	41	35–47	29	23–35	**43**	**36–49**	**35**	**28–41**
Extent (age-standardized)																
Localized	74	70–78	55	49–60	85	81–88	64	58–69	80	75–83	65	59–70	**84**	**80–87**	**70**	**64–75**
Local/regional spread	55	51–59	23	19–27	56	52–61	24	20–28	65	60–69	27	23–32	**68**	**63–72**	**37**	**32–42**
Distant metastasis	11	9–13	1	0–1	15	12–17	2	1–3	17	14–20	2	1–4	**21**	**18–23**	**3**	**2–4**
Unknown	21	15–27	12	7–18	27	20–35	9	5–16	32	25–40	17	11–23	32	26–38	15	10–21

[a]Statistically significant changes between periods 1995–1999 and 2010–2014 are in bold.

proportion of cases with death certificate only and diagnosed at autopsy remained low (2%) for the whole period. In general, 44% of cases were diagnosed at age 50–69 and 47% of the cases at age ≥70 years. The proportion of GC cases aged ≥70 years increased from 1995–1999 to 2010–2014 by 14% and decreased in other age groups. There were approximately 10% more GC cases among men and the difference did not change during the study period. In total, 65% of cases were non-cardia cancers and 7% were cardia cancers. Around half of the cases (49%) were adenocarcinomas. 40% of GC cases were diagnosed with distant metastasis. The proportion of localized and locally/regionally spread cancer was 24%. In total, 12% of cases had unknown extent (Table 1).

From 1995 to 2014, the age-standardized incidence decreased for both men (APC −2.6%) and women (APC −2.4%) (Figure 1). The age-specific incidence decreased for patients under 70 years old (15–49 years old APC −3.0%; 50–69 years old APC −3.1%). A steady decline in age-standardized incidence was also seen for adenocarcinomas (APC −1.7%), NOS (APC −5.7%) and cases with other morphology (APC −2.7%). The incidence trend of non-cardia cases declined significantly only until 2005 (1995–2005 APC −4.1%). At the same time, the incidence of unspecified cases declined slightly from the beginning of the study period and made a sharp decline from 2008 (2008–2014 APC 19.7%). Age-standardized trends showed a significant decrease for localized (APC −2.5%), locally/regionally spread (APC −2.8%), and GC cases with distant metastasis (APC −3.2%). There were no significant changes for cases with unknown extent of disease.

Survival

The 1-year and 5-year RSR estimates for GC in 1995–2014 are shown in Table 2. In general, since 1995, 1-year and 5-year age-standardized RSR of GC increased significantly by 10% and 8%, respectively. During the last study period (2010–2014), the age-standardized 1-year RSR was 48% and 5-year RSR was 28%. Survival was higher for females and increased significantly by 10% during the whole study period, while the survival of men improved by 6%. The survival increased significantly for age group 50–69 but there was also general improvement in other age groups. In the last study period (2010–2014), the 5-year RSR was 31% for patients aged 50–69 years and 22% for those aged ≥70 years. There were no significant changes in survival by disease subsite; however, the survival was highest for non-cardia cancers. According to morphology, survival improved for other type of GC cases, while no significant changes in survival were seen for adenocarcinomas, signet cell carcinomas and NOS. As expected, the survival was highest for cases with localized extent and lowest for cases with distant metastasis. A large gain in 5-year survival was seen for localized (by 15%) and locally/regionally spread disease (14%). However, only a small survival improvement by 2% was seen for GC cases with distant metastasis.

Survival by the extent of disease

The 5-year RSR for localized and locally/regionally spread cancer in 1995–1999 and 2010–2014 is presented in more detail in Table 3. 5-year RSR for GC patients with localized disease increased significantly from 1995–2014 in females (23%), the age group 50–69 years (15%), and in cases where morphology was classified as 'other'. In patients with locally/regionally spread disease, the survival increased significantly for men (15%), age group 50–69 years (14%) and ≥70 years (15%) as well as in cases with non-cardia (11%) and unspecified morphology (25%). No remarkable changes in 5-year

Table 3. Five-year relative survival ratios (RSR) for localized and locally/regionally spread stomach cancer in Estonia, by sex, age, subsite and morphology in 1995–1999 and 2010–2014.

	Localized					Local/regional spread				
	1995–1999 5-year RSR	95% CI	2010–2014 5-year RSR	95% CI	Change[b]	1995–1999 5-year RSR	95% CI	2010–2014 5-year RSR	95% CI	Change[b]
Sex										
Male	58	51–65	63	55–70	+5	21	16–26	36	30–43	**+15**
Female	53	46–60	76	68–83	**+23**	26	20–32	37	29–45	+11
Age at diagnosis										
15–49	80	67–89	87	69–95	+7	27	17–38	44	28–59	+17
50–69	59	52–65	74	66–81	**+15**	27	21–32	41	34–49	**+14**
70+	46	37–54	63	54–71	+17	17	12–24	32	24–40	**+15**
Subsite										
Cardia	43	23–62	59	36–79	+16	28	15–44	26	14–40	−2
Non-cardia	62	56–68	69	63–75	+7	27	22–32	38	32–44	**+11**
Unspecified	39	30–49	73	58–86	+34	13	8–19	38	25–52	**+25**
Morphology[a]										
Adenocarcinoma	62	55–69	70	62–77	+8	26	21–32	38	31–45	+12
Signet cell carcinoma	59	50–68	61	50–70	+2	22	15–29	33	25–41	+11
Other	38	24–53	86	72–96	**+48**	23	14–34	49	32–65	+26

[a]NOS not shown, small numbers.
[b]Significant changes in bold.

RSR were seen in GC patient subgroups with distant metastasis and unknown extent of GC.

Discussion

In this population-based study in Estonia, an overall decreasing trend of GC incidence from 1995 was seen. This is in good accordance with European data [6], but not with USA [20] and Asia [1], where the reported incidence of GC is still high or even increasing. In our study, a shift in the age distribution toward the elderly was seen. An increased number of elderly cancer patients is similar to other studies [8,10,14,21], mainly due to the ageing of European population.

Likewise to our study, other European studies [2,8,10,11] have described higher incidence of GC among men. The direct cause of this gender difference is unknown, but higher GC incidence may be influenced by divergent smoking patterns [5] and body mass indices [20,22] in the past. In fact, there are more smokers and persons with higher BMI among men in Estonia [23].

The incidence of cardia cancer is rising in USA [20], which is mainly attributed to obesity [20,22]. And even though the general proportion of people with high BMI is also rising in Estonia [23] and in Europe [24], there is no change in the incidence of cardia cancer in Europe [10,11] as well as in our study. In contrast, our data revealed that the incidence of non-cardia cancer significantly decreased from 1995–2005 by 4% per year. Non-cardia cancer is mostly caused by *H. pylori* infection [3] that has declined in Europe for the last decades [25]. Therefore, it might be one of the reasons for GC decline seen in our study as well. Indeed, triple therapy against *H. pylori* was introduced in Estonia in 1999 [26], and, for example, the prevalence of *H. pylori* has declined among children aged 0–14 from 42% in 1991 to 28% in 2002 [27].

During the whole study period, the proportion of GC cases diagnosed with distant metastasis was still high, although the incidence of these cases declined annually by 3.2%. To detect new cancer cases at the early stages, a screening program for GC is used in Asia, where the incidence but also the proportion of cases diagnosed in localized extent is high. Nonetheless, it is suggested that screening programs are only cost-effective in countries with high GC incidence [28], and therefore screening programs are not launched in a number of other countries, including Estonia.

The survival of GC in Estonia has improved over time (5-year RSR from 20% to 28%) reaching the level of Northern European countries in 2010–2014 (e.g. 26% in Finland, 25% in Sweden, 27% in Norway) [9]. Although there are studies that show no improvement in survival like in the Netherlands [10], Finland, Italy, and France [9], the general survival of GC in Europe is rising [8,9,11,21]. Our study results are in line with these general European trends.

In our study, the survival was better for women. Although 5-year RSR improved significantly for both men and women, the gap between genders increased during the study period. The better survival among women is in good accordance with previous European studies [8,12] and a previous study in Estonia [29], where the survival of GC among women remained high even after the adjustment for age, stage, and subsite. Furthermore, the 5-year RSR among women in Estonia is approximately 4% higher than in Nordic countries like Finland, Sweden and Norway [30]. The reasons for higher survival among women are not clear but it has been suggested that the estrogen receptors in cancer tissue have a protective effect against the invasiveness of GC in females [31]. Studies have also found that males have more cardia cancer [10,11], which is similar to our study where the proportion of cardia cancer among men was 3.5% higher than among women (data not shown). The cardia cancer itself has different risk factors (e.g. being overweight) and lower survival rates compared to other subsites [8,10,11,14]. Therefore, higher occurrence of cardia cancer could influence the lower survival of GC among Estonian men.

In general, we found that survival was better for patients younger than 50 years, although the survival in this age group did not significantly improve over the study period. In contrast, the 5-year RSR of 50–69-year-old patients increased

significantly from the first study period and contributed mostly to the survival gain seen in GC patients. Among the elderly (70 years and older), the increase in survival was also visible, although, it is important to note that their 5-year RSR was still lower than in other studied age groups. Moreover, the gap between survival of younger and elderly patients was present for every extent of disease at diagnosis. Several studies have presented similar results [8,13,14,21] and have found factors that exclude necessary treatments for older patients [13,32,33]. Whether under-treatment, some other factors like comorbidities and generally worse performance status are the reasons for lower survival of elderly GC patients in Estonia is not currently known.

As expected, 5-year survival was higher for cases diagnosed at early stage of GC (localized and locally/regionally spread) and the survival improved significantly during the study period. The 5-year survival of metastatic disease improved only from 1% to 3%. Similar lower survival rates of metastatic disease have been reported in other European countries like Germany and the Netherlands [10,14]. Nevertheless, compared to German data from 2000–2006 [14], the 5-year RSR in our study (2000–2004) was approximately 12 percentage units lower in localized GC cases, 3 percentage units lower in locally/regionally spread cases, and even 5 percentage units lower in GC cancer patients with distant metastasis, showing substantial room for further improvements.

The general GC survival gain seen in our study was mainly due to survival improvement in localized and locally/regionally spread GC. The main changes that could have had an impact on the survival of localized and locally/regionally spread GC were improvements in surgery techniques (e.g D2 lymphnode dissection), and changes in standard treatment like chemoradiation [34] and perioperative chemotherapy [35] (the results of milestone trials were published in 2001 and 2006, respectively). Also, the mandatory multidisciplinary team meetings were introduced in Estonia in 2009 that was followed by the reimbursement of these meetings by The Estonian Health Insurance Fund since 2012. Clearly, it has contributed to better of GC survival as well. Despite of some success in localized and locally/regionally spread GC, the low survival of metastasized GC cases is still an unresolved problem.

This nation-wide study was based on ECR that covers the whole Estonian population and has a high completeness and validity [36,37]. Therefore, it was possible to describe the incidence and survival by sex, age, subsites, morphology, and the extent of the disease of the whole population during a 20-year period. The previous studies based on ECF data have used same methodology [38–40]. However, there are a number of limitations in our study. One of these is the proportion of GC cases with unknown morphology or extent of disease, which could have influenced incidence and survival estimates. The survival of cases with unknown extent was much higher than the survival of cases with distant metastasis. Therefore, it seems that not only cases with more advanced stages were registered as diseases with unknown extent. Some of the stage-specific survival improvement may have been due to stage migration as a result of more accurate diagnostic procedures. Furthermore, this study did not include information about other possible factors that could have an impact on the incidence or survival rates of GC, e.g. smoking, eating-drinking habits, and comorbidities.

Taken together, our study showed that the incidence of GC in Estonia has significantly declined and general survival improved from 1995–2014. Nevertheless, the developments in diagnostics and treatments have mostly improved the survival of cases with early disease and in the age group of 50–69 year's old patients. To further improve the survival of GC in Estonia, the problematic areas revealed in our study (lower survival among men, elderly patients and metastatic cases) should be addressed. Based on this population-based study of GC survival in Estonia, a highly detailed quality-indicator-based analysis that will also include data about treatment of individual GC patients in Estonia is already planned.

Disclosure of interest

The authors report no conflict of interest.

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