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Regional and socioeconomic variation in survival of patients with oesophagus, cardia and stomach cancer in Denmark, 2013-2017. The Benchmark III project.

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Abstract

Introduction: This article explores variation in the survival and mortality of Danish patients with oesophagus, cardia and stomach cancer, 2013-2017, in relation to their region of residence and socioeconomic status.

Methods: Data were extracted from The Danish Clinical Registry of Carcinomas of the Oesophagus, the Gastro-Oesophageal Junction and the Stomach (DECV), a clinical register, based on reports from hospital departments and designed for clinical quality improvement. The analysis included covariates at person-, tumour-, and treatment levels. A cohort analysis was implemented to quantify the variations in mortality and identify possible underlying mechanisms behind regional and socioeconomic variations.

Results: The mortality of female oesophagus, cardia and stomach cancer patients varied between the five Danish regions with HRs of 1.26 (1.07-1.49) between the regions with highest and lowest mortality. The regional variation in mortality of female patients was attributable to underlying variation in tumour stage and treatment, and it was not confounded by other covariates. Among male patients there was less regional variation, but some difference between regions emerged with adjustment for stage and treatment. Mortality was lowest in male and female patients with high income and high education. The gradient of mortality with income was much attenuated with adjustment for treatment. The weaker gradient with education was strengthened by adjustment for tumour stage.

Conclusion: The results of these analyses point to potentially important regional and socioeconomic differences in the mortality outcomes of Danish patients with oesophagus, cardia and stomach cancers. The regional and socioeconomic variations reflect differences in stage distribution and in access to treatment. There are some internal inconsistencies in the results, with different associations in men and women, and with different associations with income and education. Overall, the results are not easy to understand and should be interpreted with caution.

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List of tables and figures

Introduction

Cancers of the upper gastrointestinal tract (oesophagus cancer [ICD10 C15] and stomach cancer [ICD10 C16]) comprise a group of aetiologically heterogeneous malignancies which in Denmark are managed at a combined oesophagus-stomach multidisciplinary team conference (MDT) (1-4).

Squamous cell cancers of the oesophagus have aetiological similarities with oral and pharyngeal cancers, and tobacco smoking and alcohol drinking are important risk factors (5). Male:female ratios are around 2.0 and in the past the incidence was higher in Copenhagen than in the rest of Denmark (6).

In the past, adenocarcinoma of the body and the distal part of the stomach was very common, but the incidence has decreased over time globally (7). The aetiology of this cancer and the reasons for the decline are not well understood, but Helicobacter pylori infection and chronic atrophic gastritis are important risk factors (8-11). The male:female ratio is close to unity (6).

Oesophageal adenocarcinoma and adenocarcinoma of the gastro-oesophageal junction has increased in incidence in recent decades and is now more frequent than both squamous cell oesophagus cancers and distal stomach cancers. The male:female ratio is about four (6). This disease is aetiologically linked with gastric reflux, Barretts oesophagus, low physical activity and obesity (12-16).

It can be difficult to separate the three cancer groups from recorded data in cancer registries because the traditional anatomy concepts are the oesophagus (C15) and the stomach (C16), thus giving little attention to the boundary between the two organs (17-19). The ICD10 classification has a code for the cardia part of the stomach (C16.0), but it is often found that many stomach cancers are coded with the unspecific "stomach cancer" code (C16.9) of which unknown proportions are cardia and more distal cancers. Similarly, a proportion of the oesophagus cancers may have unspecific codes for histology, making the distinction between squamous cell and adenocarcinomas difficult.

The age and sex standardized incidence rate (WST per 100.000 population in 2012-2016) of oesophagus and stomach cancer combined was higher in Denmark (9.4) than in Norway (7.4) and Sweden (6.0). The corresponding population mortality rates were 6.5, 4.6 and 4.5, respectively (20).

Patients under suspicion of oesophageal, cardia and stomach cancer are referred to one of the four treating centres in Denmark (21). Thorough work-up is conducted and the patient-case is

presented at the MDT where abdominal and thoracic surgeons, medical oncologists, radiologists, nuclear medicine specialists, pathologists, and specialist nurses can influence the treatment of the patient. In situations where additional specialists are warranted, these can be invited ad-hoc. At the MDT, the goal is to offer patients a well-coordinated and individualised treatment plan in accordance with the national guidelines (22).

The five government regions in Denmark are budget-holders and operationally responsible for the management and provision of healthcare services for their respective populations, and the comparison of the survival of their resident cancer patients is therefore relevant to the evaluation of the services and can inform quality improvements.

Analysis of survival in relation to socioeconomic factors addresses the issue of equity in access to care as one of Six Domains of Health Care Quality defined by the Institute of Medicine (23). Secondly, socioeconomic variation also plays a role as a possible case-mix covariate in the analysis and understanding of regional variation.

The present paper describes an analysis of the survival of Danish patients with oesophagus, cardia and stomach cancer, using a specialist clinical database, designed for monitoring of treatment and outcomes and clinical quality improvement (24).

Data and methods

The present analyses use cases of oesophagus, cardia and stomach cancer diagnosed in the period from 2013 to 2017 in the RKKP clinical database for oesophagus, cardia and stomach cancers: The Danish Clinical Registry of Carcinomas of the Oesophagus, the Gastro-Oesophageal Junction and the Stomach (DECV) (24). In this report we use the term "cardia" to denote cancers of the gastro-oesophageal junction.

The data are based on reports from surgical and oncological hospital departments. The formats of the reports are specific to this database. There are separate report forms for the three subtypes, and the choice of form is guided by the Siewert classification (25). Historically there has been some variation in classification of the adenocarcinomas of the gastro-oesophageal junction, where some centres classified all adenocarcinomas of the oesophagus as gastro-oesophageal junction cancers, but most centres classified the adenocarcinomas according to the Siewert classification.

The principal epidemiological analyses in this report address the all-cause mortality of patients with oesophagus, cardia and stomach cancer in relation to their region of residence and their socioeconomic status. Mortality information was linked to the database from the central Danish population register.

Data about household income, education, civil status, and comorbidity was obtained by linkage with Statistics Denmark, the Central Person Register, and the National Hospital Discharge Register, respectively (26-29). This is feasible due to the unique personal identification number, which every citizen in Denmark is given at birth or immigration.

Household income per person in the year before cancer diagnosis was analysed by quartiles of the income distribution for patients with oesophagus, cardia and stomach cancer, separately for men and women.

The highest attained education for each person was classified as basic school education (the compulsory school education only); professional education (including for example apprenticeships and including high-school only); shorter further education; and longer further education.

Civil status was classified as: married or in registered partnership; other cohabiting persons; single.

Comorbidity was characterised by the Charlson index (30), computed based on hospital discharge diagnoses in the 10-year period before the cancer diagnosis.

Missing values were analysed as a separate category.

A cohort analysis was conducted of the occurrence of deaths in the personyears experience from date of cancer diagnosis until death, emigration or end-of-follow-up on 8th October 2018. This was implemented as a Cox regression model with time since date of diagnosis as the principal time dimension. Analyses were conducted for men and women separately, and the basic models included age (continuous quadratic function to account for the non-linear association between age and mortality), sex, and year of diagnosis (categorical) as covariates. Further covariates were added separately to the basic model in order to identify confounding or mediating characteristics.

Results

Tables 1a and 1b describe the study population. There were 5,229 patients (3,697 men and 1,532 women) diagnosed with cancer of oesophagus (893 men and 451 women), cardia (2,155 men and 539 women) or stomach (649 men and 542 women) in 2013-2017. The male:female ratio was 2.0 for oesophagus, 4.0 for cardia and 1.2 for stomach cancer.

Most patients were in their 60s and 70s and about half of the patients had a record of comorbidity. Socio-economic characteristics varied between the five regions, with the highest levels of education and income in patients in Region Hovedstaden, the capital area of the country.

Tumour stage was most often stage III or IV. The proportion of patients with no data on stage was high in Region Midtjylland (32%). Nordjylland had the highest proportion of early stage cancers: 37% of the staged cancers were stage I-II in Nordjylland vs. the national figure of 27%. Region Hovedstaden had the lowest proportion of stage IV cancers (41% vs. 45% nationally), and the highest proportion of stage IV cancers (among the staged cases) was in Region Midtjylland (56%).

The distribution of cancer type varied between regions, mainly due to differences between oesophagus and cardia proportions. For men, Nordjylland had many cardia cancers (62%) and few oesophagus (17%), and Midtjylland the opposite: 53% cardia and 30% oesophagus cancers. Among women it was mainly Region Hovedstaden that differed from the other regions, with a higher proportion of cancers of oesophagus (35%) and a lower proportion of cardia cancers (30%).

The recorded cancer treatment was complex, involving surgical resection, chemotherapy, radiation, and combinations of these. Pooling the data in men and women, we have computed that the use of active treatments varied from 76% in Hovedstaden to 64% in Nordjylland Treatments that involved surgical resection were highest in Nordjylland (36%) and lowest in Syddanmark (31%) and Hovedstaden (32%). Non-surgical treatments were highest in Sjælland (40%) and Hovedstaden (44%), and lowest in Nordjylland (27%). Treatments with chemotherapy or combinations that included chemotherapy were highest in Sjælland (60%) and Hovedstaden (57%), and lowest in Nordjylland (47%). Treatments with radiotherapy or combinations with radiotherapy were highest in Hovedstaden (32%) and lowest in Nordjylland (14%).

Figure 1 shows the Kaplan-Meier survival functions for the five regions, separately for men and women. In female patients, there was variation in survival between the regions, with lowest survival in Region Syddanmark and Region Midtjylland.

Table 2 shows the results of the cohort analysis of patient mortality for each variable separately, but with each model adjusted for age, calendar year and comorbidity. Mortality was highest in older patients and patients with comorbidity. Some variation in mortality between the regions was seen in women, with the highest mortality rates in Region Midtjylland, Syddanmark and Sjælland. In men, there was less variation between the regions.

Mortality was highest in single persons and in cohabiting men, and mortality tended to be highest for persons with low income.

Mortality was highest in patients with oesophagus cancer and lowest in patients with cardia cancer. Mortality was high with advanced tumour stage. Patient groups defined by their treatment had lowest mortality among those with surgical resection (HRs in range 1.00-3.15), intermediate among those with other active treatments (range 3.64-8.18), and highest in patients with no active treatment (range 11.40-13.54).

The variation in mortality between residents in the regions is explored further in Table 3.

In women, there was statistically significant variation in mortality between the regions, and adjustment for socioeconomic variables (civil status, education and income) or cancer type did not influence the parameter estimates for region of residence, but adjustment for stage or for treatment attenuated the regional variation very much, and the excess mortalities in women in Midtjylland, Syddanmark and Sjælland in Model 1 was thus attributable to underlying variation in stage or treatment distribution between the regions. The stage and treatment estimates were highly correlated, and the mutually adjusted estimates were generally closer to unity than the not-mutually-adjusted estimates (data not shown). It was therefore not possible to separate the effects of variation in stage and variation in treatment on the regional differences in mortality in female patients.

The pattern was different in male patients, where there was little variation between regions in Model 1. Adjustment for stage and treatment changed the estimates, and in the stage-adjusted model it appeared that patients in Hovedstaden had higher mortality than patients in the other four regions when their more favourable stage-distribution was considered. Further adjustment for treatment strengthened the difference in mortality between male patients in Hovedstaden and the rest of the country.

Table 4 shows the principal comparison of the regions (from Table 3), but now stratified by cancer type. In Table 3 there was no sensitivity of estimates to statistical adjustment for cancer type, and the stratified analyses showed patterns that were broadly consistent with the overall result. The stratified analysis revealed less regional variation between female patients with stomach cancer than the overall analysis, and the excess mortalities in female patients in Midtjylland, Syddanmark and Sjælland (Model 1) were only seen clearly in oesophagus and cardia cancers. For stomach cancer in women, region Nordjylland had low mortality, especially when estimates were adjusted for treatment.

Tables 5 and 6 shows analyses of mortality in relation to two of the available indicators of socioeconomic status: household income per person and highest attained education. In both men and women, there were gradients whereby mortality decreased with increasing income (Table 5) and (less strongly) with increasing level of education (Table 6). The estimates were robust to statistical adjustment for tumour type. The gradient of mortality with income was much attenuated with adjustment for treatment. The weaker gradient with education was strengthened by adjustment for tumour stage.

Discussion

Main findings

We found regional variation in mortality of female patients with esophagus, cardia and stomach cancer, but there was no similar variation among male patients. Despite different aetiologies and differences in mortality between the three cancer types, the results for both men and women were not influenced by adjustment for cancer type. This indicates the absence of confounding by cancer subtype in the studied associations. We also stratified the analysis by cancer type, and the results in men were consistent with the overall results, but the excess mortalities in women in Region Midtjylland and Region Syddanmark were strongest for esophagus cancer and cardia cancer, and weakest for stomach cancer.

The mortality of patients was strongly influenced by stage and treatment, and the patterns differed between men and women. For women, the regional differences in mortality were explained by differences in stage and treatment, identifying regional variation in stage and treatment as the origin of the regional variation. In male patients, the pattern of similar mortality rates in the regions was changed with statistical adjustment for stage and treatment and in the adjusted models a pattern emerged with higher mortality in Region Hovedstaden due to a more favorable stage distribution in this region.

It remains as a distinct weakness of this study that we were unable to disentangle separate effects of stage and treatment on the regional variation in mortality of female patients. The high proportion of records with missing value for stage is also a major limitation.

Patterns in men and women and in the three cancer subtypes

The variation in mortality patterns and associations between male and female patients was somewhat surprising. The analysis plan prespecified that males and females would be analysed separately, but the expectation was that regional and socioeconomic variations in patient case mix and in treatment patterns would be similar in the two sexes. On the other hand, we considered before the data analysis that pooling of the three cancer subtypes could possibly be too crude, given the known differences in treatment and survival. The adjusted and the stratified analyses give support to the combined approach.

Based on the observed results, we consider that the finding of regional variation in survival in one sex only can be considered as a lack of consistency and reproducibility, hence giving some reservation on the internal validity of the results.

The definition of the three cancer subtypes is not clearly defined in the clinical database, and there is evidence of some variation in coding of cancer subtype between the regions. We expect that there is some systematic variation in the classification between regions between oesophagus and cardia, and between cardia and stomach. By far, most adenocarcinomas of the oesophagus and gastro-oesophageal junction are located at the junction. The registration of adenocarcinomas in the oesophagus and cardia has not been uniform in Denmark. This has led to some misclassification, but it is evident from the literature that the frequency of adenocarcinomas truly of the oesophagus is very low (1.0-2.4% [31-32]) compared with junctional adenocarcinomas, so in the greater picture this bias will barely skew the results of the analyses. In the presence of such differential classification of subgroups, the analytical strategy will typically prescribe a pooled analysis, and based on the robustness of results to statistical adjustment for cancer type we are confident that the results are a fair representation of reality.

Variation between socioeconomic groups

Like other studies we found a social gradient with lowest mortality in patients with long education or high income (33-34). The results show that these variations were mainly due to more favourable stage distribution and more intensive treatment in the more affluent patients.

Our results indicate that socioeconomic position is a prognostic factor, but importantly it did not contribute to the regional differences in mortality. We explored education and income as

socioeconomic indicators, and they may be prognostic markers in different parts of the causal pathway. Education level has a correlation to stage and for women also to cancer type. The education gradient was strengthened when further adjusted for stage and for cancer type for women (Table 6). Education may be indicating a person's receptiveness and empowerment to act on health education messages, and most importantly to access appropriate health services (35).

Further in the causal pathway is income (in our analysis defined as disposable income per adult person in the household). Income has been reported to be a stronger predictor of survival than education (36). Income is a direct measure of material resources (35). In our case the income gradient was attenuated when adjusted for treatment and for men also when adjusted for stage. This may indicate a relationship between affluence and access to active treatment, even in the Danish tax-financed health care system. This pattern has also been reported for other cancer types, for example lung cancer (37-38). The high mortality in single male patients points to the possible prognostic importance of social characteristics apart from education and income.

Overall, there are some internal inconsistencies in the results, with different associations in men and women, and with different associations with income and education. We consider that the results are not straightforward and easy to understand and should therefore be interpreted with caution.

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Table 1a. Overview of cohort of 3697 men with oesophagus, cardia and stomach cancer, Denmark, 2013-2017.

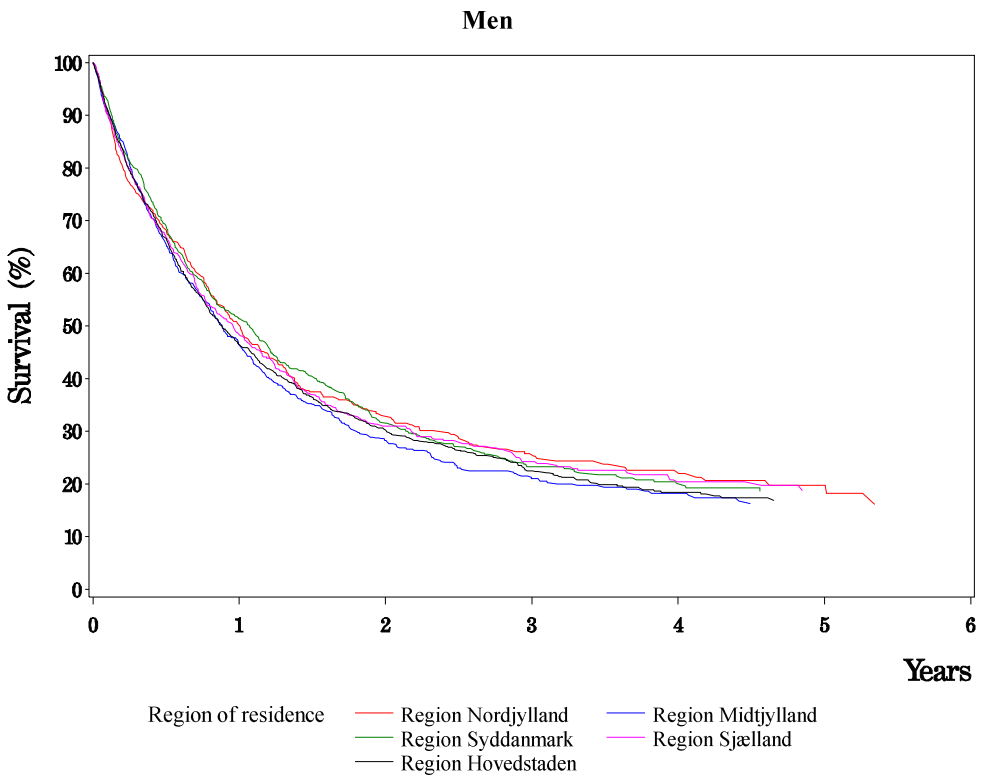
	Nordjylland		Midtjylland		Syddanmark		Sjælland		Hovedstaden		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Year of diagnosis (p=0.52)												
2013	61	15	141	18	161	19	122	19	211	21	696	19
2014	92	22	159	21	166	19	132	20	199	20	748	20
2015	83	20	145	19	165	19	127	20	224	22	744	20
2016	92	22	162	21	183	21	138	21	192	19	767	21
2017	89	21	163	21	177	21	126	20	187	18	742	20
Age group (p=0.002)												
0-49	14	3	19	2	29	3	29	4	51	5	142	4
50-59	64	15	92	12	128	15	96	15	156	15	536	14
60-69	115	28	286	37	267	31	227	35	320	32	1215	33
70-79	126	30	238	31	276	32	202	31	334	33	1176	32
80-89	84	20	124	16	136	16	79	12	134	13	557	15
90+	14	3	11	1	16	2	12	2	18	2	71	2
Charlson comorbidity index (p=0.46)												
0	230	55	410	53	465	55	353	55	534	53	1992	54
1-2	127	30	233	30	258	30	185	29	286	28	1089	29
3+	60	14	127	16	129	15	107	17	193	19	616	17
Civil status (p=0.44)												
Married	245	59	482	63	528	62	405	63	589	58	2249	61
Cohabiting	104	25	174	23	210	25	148	23	267	26	903	24
Single	68	16	114	15	114	13	92	14	157	15	545	15
Education (p<0.0001)												
School	191	46	269	35	322	38	234	36	292	29	1308	35
Professional education	154	37	371	48	387	45	291	45	469	46	1672	45
Shorter further education	56	13	76	10	88	10	85	13	142	14	447	12
Longer further education	10	2	34	4	30	4	23	4	82	8	179	5
NA	6	1	20	3	25	3	12	2	28	3	91	2
Income (median) (p<0.0001)												
Quartile 1 (125,303)	104	25	189	25	254	30	162	25	215	21	924	25
Quartile 2 (159,097)	133	32	188	24	208	24	159	25	236	23	924	25
Quartile 3 (195,663)	110	26	204	26	212	25	165	26	233	23	924	25
Quartile 4 (300,859)	70	17	189	25	178	21	159	25	329	32	925	25
Cancer type (p<0.0001)												
Oesophagus	72	17	228	30	183	21	145	22	265	26	893	24
Cardia	260	62	411	53	511	60	392	61	581	57	2155	58
Stomach	85	20	131	17	158	19	108	17	167	16	649	18
Tumour stage (p<0.0001)												
I-II	135	32	140	18	167	20	123	19	249	25	814	22
III	79	19	105	14	237	28	205	32	280	28	906	25
IV	157	38	287	37	303	36	244	38	387	38	1378	37
NA	46	11	238	31	145	17	73	11	97	10	599	16
Treatment (p<0.0001)												
Resection	44	11	97	13	61	7	30	5	67	7	299	8
Resection and chemoterapy	95	23	81	11	194	23	141	22	190	19	701	19
Resection and radiation	3	1	7	1	3	0	1	0	0	0	14	0
Resection, chemoterapy and radiation	14	3	91	12	33	4	43	7	61	6	242	7
Chemoterapy	69	17	132	17	129	15	139	22	210	21	679	18
Radiation	22	5	38	5	74	9	44	7	117	12	295	8
Chemoterapy and radiation	22	5	83	11	90	11	75	12	137	14	407	11
None	148	35	241	31	268	31	172	27	231	23	1060	29
Total	417	11	770	21	852	23	645	17	1013	27	3697	100
Incidence rate per 100,000, oesophagus	3.9		6.2		7.0		8.4		8.3		7.1	
Incidence rate per 100,000, cardia and stomach	9.2		6.3		6.3		6.0		6.2		6.6	
Mortality rate per 100,000, oesophagus	2.6		5.2		4.7		6.6		5.1		5.0	
Mortality rate per 100,000, cardia and stomach	6.2		3.3		4.8		2.9		3.8		4.0	

p-values are from Chi-square tests for heterogeneity.
Incidence and mortality rates are per 100,000 resident population and age-standardised (World, Segi), 2011-2015.
The cancer type classification in the body of the table and in the main analysis, and the cancer type classification for population rates are not identical.

Table 1b. Overview of cohort of 1532 women with oesophagus, cardia and stomach cancer, Denmark, 2013-2017.

	Nordjylland		Midtjylland		Syddanmark		Sjælland		Hovedstaden		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Year of diagnosis (p=0.28)												
2013	27	18	66	20	74	20	42	18	69	16	278	18
2014	28	18	59	18	89	24	51	22	96	22	323	21
2015	28	18	60	18	65	17	38	16	94	21	285	19
2016	38	25	67	20	91	24	55	24	92	21	343	22
2017	32	21	77	23	55	15	48	21	91	21	303	20
Age group (p=0.05)												
0-49	8	5	16	5	15	4	16	7	20	5	75	5
50-59	20	13	31	9	41	11	35	15	45	10	172	11
60-69	41	27	83	25	95	25	85	36	145	33	449	29
70-79	49	32	115	35	123	33	53	23	141	32	481	31
80-89	28	18	67	20	83	22	39	17	77	17	294	19
90+	7	5	17	5	17	5	6	3	14	3	61	4
Charlson comorbidity index (p=0.09)												
0	80	52	208	63	203	54	131	56	243	55	865	56
1-2	49	32	79	24	123	33	72	31	122	28	445	29
3+	24	16	42	13	48	13	31	13	77	17	222	14
Civil status (p=0.77)												
Married	71	46	145	44	176	47	109	47	189	43	690	45
Cohabiting	46	30	103	31	126	34	73	31	153	35	501	33
Single	36	24	81	25	72	19	52	22	100	23	341	22
Education (p<0.0001)												
School	82	54	172	52	201	54	104	44	172	39	731	48
Professional education	46	30	89	27	116	31	81	35	152	34	484	32
Shorter further education	21	14	51	16	40	11	40	17	74	17	226	15
Longer further education	1	1	5	2	5	1	3	1	27	6	41	3
NA	3	2	12	4	12	3	6	3	17	4	50	3
Income (median) (p<0.0001)												
Quartile 1 (109,800)	50	33	90	27	104	28	51	22	88	20	383	25
Quartile 2 (153,500)	40	26	90	27	116	31	52	22	85	19	383	25
Quartile 3 (177,386)	35	23	77	23	87	23	61	26	123	28	383	25
Quartile 4 (247,371)	28	18	72	22	67	18	70	30	146	33	383	25
Cancer type (p=0.07)												
Oesophagus	39	25	90	27	100	27	67	29	155	35	451	29
Cardia	64	42	126	38	135	36	82	35	132	30	539	35
Stomach	50	33	113	34	139	37	85	36	155	35	542	35
Tumour stage (p<0.0001)												
I-II	48	31	59	18	76	20	40	17	116	26	339	22
III	21	14	27	8	75	20	64	27	126	29	313	20
IV	58	38	128	39	141	38	87	37	145	33	559	36
NA	26	17	115	35	82	22	43	18	55	12	321	21
Treatment (p<0.0001)												
Resection	16	10	33	10	15	4	15	6	33	7	112	7
Resection and chempterapy	29	19	33	10	62	17	41	18	66	15	231	15
Resection and radiation	2	1	3	1	0	0	0	0	3	1	8	1
Resection, chenoterapy and radiation	5	3	28	9	7	2	16	7	39	9	95	6
Chemoterapy	28	18	54	16	69	18	53	23	69	16	273	18
Radiation	8	5	16	5	32	9	20	9	53	12	129	8
Chemoterapy and radiation	5	3	23	7	46	12	21	9	57	13	152	10
None	60	39	139	42	143	38	68	29	122	28	532	35
Total	153	10	329	21	374	24	234	15	442	29	1532	100
Incidence rate per 100,000, oesophagus	1.7		1.6		2.1		2.3		2.5		2.1	
Incidence rate per 100,000, cardia and stomach	3.7		2.9		3.1		3.0		2.9		3.0	
Mortality rate per 100,000, oesophagus	0.5		1.4		1.3		1.5		1.2		1.2	
Mortality rate per 100,000, cardia and stomach	2.2		1.4		2.2		2.1		1.7		1.9	

p-values are from Chi-square tests for heterogeneity.
Incidence and mortality rates are per 100,000 resident population and age-standardised (World, Segi), 2011-2015.
The cancer type classification in the body of the table and in the main analysis, and the cancer type classification for population rates are not identical.


Men
Survival (%)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
Years
Region of residence
Region Nordjylland
Region Midtjylland
Region Syddanmark
Region Sjælland
Region Hovedstaden

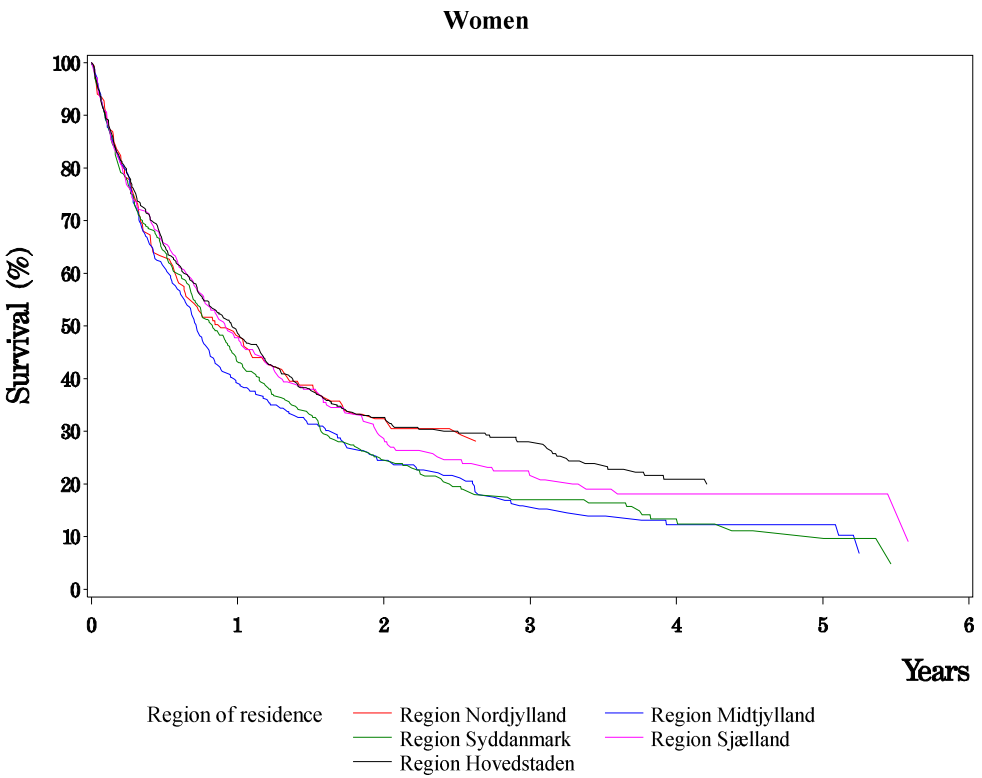

Women
Survival (%)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
Years
Region of residence
Region Nordjylland
Region Midtjylland
Region Syddanmark
Region Sjælland
Region Hovedstaden

Table 2. Cox regression analysis of all-cause mortality in relation to the available variables on male and female patients with oesophagus, cardia and stomach cancer, Denmark, 2013-2017

	Men		Women	
	HR	95% CI	HR	95% CI
Year of diagnosis		p=0.12		p=0.44
2013	1.00		1.00	
2014	0.91	0.81-1.02	0.97	0.82-1.16
2015	0.87	0.78-0.98	0.91	0.76-1.10
2016	0.89	0.79-1.00	0.86	0.71-1.03
2017	0.86	0.76-0.98	0.89	0.73-1.09
Age group		p<0.0001		p<0.0001
-49	0.67	0.54-0.84	0.81	0.61-1.09
50-59	0.84	0.74-0.95	0.73	0.59-0.90
60-69	0.82	0.75-0.90	0.72	0.62-0.84
70-79	1.00		1.00	
80-89	1.61	1.44-1.80	1.51	1.29-1.77
90+	2.49	1.95-3.18	2.49	1.89-3.30
Charlson comorbidity index		p<0.0001		p=0.0004
0	1.00		1.00	
1-2	1.05	0.96-1.05	1.14	1.00-1.30
3+	1.26	1.13-1.39	1.39	1.18-1.64
Region of residence		p= 0.18		p= 0.02
Nordjylland	0.90	0.79-1.03	0.99	0.79-1.24
Midtjylland	1.02	0.92-1.14	1.26	1.07-1.49
Syddanmark	0.91	0.82-1.01	1.21	1.03-1.42
Sjælland	0.98	0.87-1.10	1.17	0.97-1.41
Hovedstaden	1.00		1.00	
Civil status		p<0.0001		p=0.17
Married	1.00		1.00	
Cohabiting	1.32	1.20-1.45	1.01	0.88-1.17
Single	1.40	1.24-1.59	1.20	0.99-1.45
Education		p=0.47		p=0.23
School	1.00		1.00	
Professional education	0.97	0.98-1.06	0.92	0.80-1.05
Shorter further education	0.95	0.84-1.08	0.91	0.76-1.09
Longer further education	0.91	0.75-1.10	0.79	0.54-1.17
NA	1.16	0.92-1.47	0.73	0.52-1.02
Income		p=0.0003		p=0.01
Quartile 1	1.00		1.00	
Quartile 2	1.13	1.01-1.25	0.93	0.79-1.09
Quartile 3	1.06	0.95-1.18	1.03	0.84-1.21
Quartile 4	0.89	0.79-1.00	0.79	0.67-0.94
Cancer type		p<0.0001		p=0.10
Oesophagus	1.27	1.16-1.40	1.16	1.00-1.34
Cardia	1.00		1.00	
Stomach	1.14	1.03-1.26	1.13	0.98-1.29
Tumour stage		p<0.0001		p<0.0001
I-II	1.00		1.00	
III	1.68	1.48-1.91	1.86	1.52-2.29
IV	5.61	4.99-6.31	4.82	4.02-5.78
NA	2.70	2.36-3.10	2.82	2.31-3.45
Treatment		p<0.0001		p<0.0001
Resection	1.55	1.26-1.92	1.07	0.73-1.56
Resection and chemoterapy	1.00		1.00	
Resection and radiation	3.15	1.76-5.62	2.72	1.19-6.24
Resection, chemoterapy and radiation	1.29	1.03-1.61	1.38	0.96-1.99
Chemoterapy	5.48	4.72-6.36	5.35	4.16-6.87
Radiation	8.18	6.85-9.77	6.67	4.98-8.94
Chemoterapy and radiation	3.64	3.09-4.30	3.69	2.79-4.88
None	13.54	11.63-15.76	11.40	8.87-14.66

Estimates for age group, year of diagnosis and Charlson index are mutually adjusted.
All other estimates are adjusted for age, year of diagnosis and Charlson index.
p-values are for heterogeneity in the adjusted models

Table 3. Cox regression analyses of all-cause mortality in relation to region of residence of male and female patients with oesophagus, cardia and stomach cancer, Denmark, 2013-2017. Sensitivity analyses for available covariate

	Model 1		Model 1 and civil status		Model 1 and education		Model 1 and income		Model 1 and cancer type		Model 1 and stage		Model 1 and treatment		Model 1 and stage and treatment		All covariates	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Males:																		
Region of residence	p= 0.18		p=0.15		p=0.15		p=0.08		p=0.35		p=0.08		p=0.0008		p<0.0001		p<0.0001	
Nordjylland	0.90	0.79-1.03	0.90	0.79-1.03	0.90	0.78-1.03	0.87	0.76-1.00	0.91	0.80-1.05	0.89	0.78-1.02	0.88	0.77-1.01	0.84	0.73-0.96	0.83	0.72-0.95
Midtjylland	1.02	0.92-1.14	1.03	0.93-1.15	1.01	0.91-1.13	1.01	0.90-1.12	1.01	0.91-1.12	0.88	0.79-0.99	1.04	0.93-1.16	0.93	0.83-1.04	0.94	0.83-1.05
Syddanmark	0.91	0.82-1.01	0.92	0.82-1.02	0.90	0.81-1.00	0.89	0.80-1.00	0.92	0.83-1.02	0.87	0.78-0.97	0.84	0.75-0.93	0.76	0.68-0.85	0.76	0.68-0.85
Sjælland	0.98	0.87-1.10	0.98	0.88-1.10	0.97	0.86-1.09	0.96	0.85-1.08	0.99	0.88-1.11	0.95	0.85-1.07	1.01	0.90-1.13	0.93	0.83-1.05	0.92	0.82-1.04
Hovedstaden	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Females:																		
Region of residence	p= 0.02		p=0.03		p=0.03		p=0.04		p=0.02		p=0.98		p=0.44		p=0.60		p=0.53	
Nordjylland	0.99	0.79-1.24	0.99	0.79-1.24	0.97	0.77-1.21	0.97	0.77-1.21	1.00	0.80-1.25	0.95	0.76-1.19	0.89	0.71-1.12	0.88	0.70-1.10	0.86	0.68-1.08
Midtjylland	1.26	1.07-1.49	1.26	1.07-1.48	1.25	1.06-1.47	1.24	1.05-1.47	1.28	1.08-1.51	1.01	0.85-1.20	1.03	0.87-1.22	1.00	0.84-1.18	1.00	0.84-1.19
Syddanmark	1.21	1.03-1.42	1.21	1.04-1.42	1.19	1.01-1.40	1.18	1.01-1.39	1.23	1.05-1.44	1.02	0.87-1.19	0.94	0.80-1.10	0.92	0.78-1.08	0.91	0.77-1.07
Sjælland	1.17	0.97-1.41	1.17	0.97-1.41	1.16	0.96-1.40	1.16	0.96-1.40	1.19	0.99-1.43	1.03	0.85-1.24	1.08	0.90-1.30	1.02	0.85-1.23	1.00	0.83-1.21
Hovedstaden	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	

Model 1 includes age, year of diagnosis and Charlson comorbidity index

Table 4. Cox regression analyses of all-cause mortality in relation to region of residence of male and female patients with oesophagus, cardia and stomach cancer, 2013-2017, Denmark. Sensitivity analyses for available covariates.

Oesophagus	Model 1		Model 1 and stage		Model 1 and treatment		Model 1 and stage and treatment	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Males:								
Region of residence	p=0.67		p=0.64		p=0.30		p=0.07	
Nordjylland	1.01	0.75-1.35	0.91	0.67-1.23	0.80	0.59-1.09	0.76	0.56-1.03
Midtjylland	0.98	0.80-1.21	0.84	0.67-1.05	1.00	0.81-1.24	0.87	0.70-1.10
Syddanmark	1.14	0.92-1.41	0.96	0.77-1.20	0.82	0.66-1.03	0.72	0.57-0.91
Sjælland	0.97	0.76-1.22	0.94	0.74-1.19	0.93	0.73-1.18	0.91	0.72-1.15
Hovedstaden	1.00		1.00		1.00		1.00	
Females:								
Region of residence	p=0.006		p=0.17		p=0.73		p=0.93	
Nordjylland	0.99	0.65-1.53	0.96	0.62-1.49	1.11	0.71-1.74	1.15	0.73-1.81
Midtjylland	1.36	1.00-1.86	1.08	0.77-1.52	1.24	0.89-1.72	1.14	0.81-1.61
Syddanmark	1.68	1.26-2.24	1.37	1.02-1.85	1.14	0.85-1.53	1.11	0.82-1.51
Sjælland	1.20	0.86-1.69	0.93	0.66-1.31	1.20	0.85-1.69	1.01	0.71-1.44
Hovedstaden	1.00		1.00		1.00		1.00	

Cardia	Model 1		Model 1 and stage		Model 1 and treatment		Model 1 and stage and treatment	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Males:								
Region of residence	p=0.10		p=0.03		p=0.02		p<0.0001	
Nordjylland	0.89	0.75-1.06	0.85	0.71-1.01	0.89	0.74-1.06	0.82	0.68-0.97
Midtjylland	1.00	0.86-1.16	0.85	0.73-0.99	0.99	0.85-1.15	0.86	0.74-1.00
Syddanmark	0.84	0.73-0.97	0.81	0.70-0.93	0.83	0.72-0.96	0.72	0.62-0.83
Sjælland	0.94	0.81-1.09	0.94	0.81-1.09	1.05	0.91-1.23	0.96	0.82-1.12
Hovedstaden	1.00		1.00		1.00		1.00	
Females:								
Region of residence	p=0.17		p=0.59		p=0.63		p=0.31	
Nordjylland	1.31	0.91-1.88	1.33	0.93-1.92	1.26	0.88-1.82	1.38	0.96-2.00
Midtjylland	1.44	1.07-1.93	1.10	0.81-1.49	0.97	0.71-1.32	0.93	0.68-1.27
Syddanmark	1.33	0.99-1.77	1.19	0.88-1.60	1.09	0.80-1.47	1.03	0.76-1.41
Sjælland	1.25	0.89-1.75	1.15	0.82-1.62	1.11	0.79-1.55	1.07	0.76-1.51
Hovedstaden	1.00		1.00		1.00		1.00	

Stomach	Model 1		Model 1 and stage		Model 1 and treatment		Model 1 and stage and treatment	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Males:								
Region of residence	p=0.50		p=1.00		p=0.38		p=0.33	
Nordjylland	0.87	0.64-1.19	0.97	0.71-1.33	0.77	0.56-1.05	0.79	0.57-1.08
Midtjylland	1.06	0.82-1.38	1.00	0.76-1.31	0.97	0.75-1.27	0.99	0.75-1.30
Syddanmark	0.96	0.75-1.24	1.00	0.80-1.29	0.83	0.64-1.08	0.83	0.54-1.07
Sjælland	1.15	0.88-1.52	1.02	0.77-1.34	0.87	0.65-1.15	0.82	0.62-1.09
Hovedstaden	1.00		1.00		1.00		1.00	
Females:								
Region of residence	p=0.25		p=0.16		p=0.003		p=0.005	
Nordjylland	0.73	0.49-1.08	0.70	0.47-1.06	0.55	0.37-0.84	0.56	0.37-0.84
Midtjylland	1.10	0.83-1.44	0.99	0.75-1.30	0.89	0.68-1.18	0.91	0.69-1.20
Syddanmark	0.96	0.74-1.26	0.80	0.61-1.05	0.70	0.53-0.91	0.70	0.54-0.92
Sjælland	1.15	0.85-1.57	1.06	0.78-1.45	1.09	0.80-1.49	1.07	0.78-1.46
Hovedstaden	1.00		1.00		1.00		1.00	

Model 1 includes age, year of diagnosis and Charlson comorbidity index

Table 5. Cox regression analyses of all-cause mortality in relation to income of male and female patients with oesophagus, cardia and stomach cancer, Denmark, 2013-2017. Sensitivity analyses for available covariates

	Model 1		Model 1 and civil status		Model 1 and education		Model 1 and region of residence		Model 1 and cancer type		Model 1 and stage		Model 1 and treatment		Model 1 and stage and treatment		All covariates	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Males:																		
Income	p=0.04		p=0.01		p=0.07		p=0.02		p=0.08		p=0.27		p=0.47		p=0.97		p=0.59	
Quartile 1	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Quartile 2	1.13	1.01-1.25	1.05	0.94-1.16	1.13	1.02-1.25	1.12	1.01-1.25	1.13	1.02-1.25	1.12	1.01-1.25	1.04	0.93-1.15	1.08	0-97-1.20	1.02	0.92-1.14
Quartile 3	1.06	0.95-1.18	1.01	0.90-1.12	1.06	0.95-1.19	1.06	0.95-1.18	1.07	0.97-1.20	1.08	0.97-1.20	0.99	0.88-1.10	1.03	0.93-1.15	0.99	0.88-1.10
Quartile 4	0.89	0.79-1.00	0.86	0.77-0.96	0.89	0.79-1.00	0.87	0.78-0.98	0.90	0.81-1.01	0.94	0.83-1.05	0.97	0.87-1.09	1.01	0.90-1.14	0.97	0.86-1.10
Females:																		
Income	p=0.03		p=0.02		p=0.09		p=0.08		p=0.03		p=0.09		p=0.19		p=0.53		p=0.58	
Quartile 1	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Quartile 2	0.93	0.79-1.09	0.90	0.77-1.06	0.92	0.78-1.08	0.92	0.79-1.08	0.93	0.79-1.09	0.92	0.78-1.08	0.90	0.77-1.06	0.92	0.78-1.08	0.86	0.73-1.02
Quartile 3	1.03	0.84-1.21	0.99	0.84-1.17	1.02	0.87-1.21	1.04	0.89-1.23	1.03	0.87-1.21	1.02	0.87-1.20	0.93	0.79-1.09	1.00	0.84-1.17	0.96	0.81-1.14
Quartile 4	0.79	0.67-0.94	0.78	0.66-0.93	0.80	0.66-0.96	0.81	0.68-0.97	0.79	0.66-0.93	0.82	0.69-0.98	0.88	0.74-1.05	0.92	0.77-1.09	0.92	0.76-1.11

Model 1 is djusted for age, year of diagnosis and Charlson comorbidity index
p-values are for the linear trend in HR over the income quartiles

Table 6. Cox regression analyses of all-cause mortality in relation to education of male and female patients with oesophagus, cardia and stomach cancer, Denmark, 2013-2017. Sensitivity analyses for available covariates

	Model 1		Model 1 and civil status		Model 1 and income		Model 1 and region of residence		Model 1 and cancer type		Model 1 and stage		Model 1 and treatment		Model 1 and stage and treatment		All covariates	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Males:																		
Education	p=0.24		p=0.63		p=0.77		p=0.17		p=0.27		p=0.003		p=0.91		p=0.39		p=0.58	
School	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Professional education	0.97	0.98-1.06	1.00	0.92-1.09	0.98	0.90-1.06	0.97	0.89-1.05	0.97	0.89-1.06	0.91	0.83-0.99	1.06	0.98-1.16	1.02	0.94-1.11	1.02	0.94-1.12
Shorter further education	0.95	0.84-1.08	0.98	0.86-1.11	0.99	0.87-1.13	0.94	0.83-1.07	0.96	0.85-1.09	0.87	0.77-0.99	1.06	0.93-1.20	0.98	0.86-1.11	0.99	0.86-1.12
Longer further education	0.91	0.75-1.10	0.96	0.79-1.16	0.99	0.82-1.21	0.89	0.73-1.08	0.90	0.74-1.09	0.81	0.67-0.98	0.91	0.75-1.11	0.90	0.74-1.09	0.92	0.75-1.12
NA	1.16	0.92-1.47	1.16	0.91-1.46	1.18	0.93-1.50	1.15	0.91-1.46	1.17	0.92-1.48	1.15	0.91-1.46	1.33	1.05-1.68	1.25	0.99-1.59	1.18	0.93-1.50
Females:																		
Education	p=0.15		p=0.19		p=0.60		p=0.26		p=0.09		p=0.06		p=0.30		p=0.19		p=0.16	
School	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Professional education	0.92	0.80-1.05	0.93	0.81-1.06	0.95	0.83-1.10	0.93	0.81-1.07	0.90	0.79-1.04	0.91	0.79-1.04	1.00	0.87-1.15	1.00	0.87-1.15	1.00	0.86-1.15
Shorter further education	0.91	0.76-1.09	0.92	0.77-1.10	0.99	0.81-1.19	0.92	0.77-1.10	0.89	0.74-1.07	0.86	0.72-1.02	0.88	0.74-1.05	0.86	0.72-1.03	0.85	0.70-1.03
Longer further education	0.79	0.54-1.17	0.81	0.54-1.19	0.91	0.61-1.37	0.85	0.57-1.25	0.78	0.53-1.16	0.82	0.55-1.21	0.98	0.66-1.46	0.95	0.64-1.41	0.96	0.63-1.45
NA	0.73	0.52-1.02	0.74	0.53-1.04	0.74	0.53-1.04	0.73	0.52-1.01	0.72	0.51-1.00	0.66	0.47-0.92	0.70	0.51-0.98	0.65	0.47-0.91	0.63	0.45-0.87

Model 1 is adjusted for age, year of diagnosis and Charlson comorbidity index
p-values are for the linear trend in HR over the non-missing education groups