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Original Article

Effect of sex on survival after resection of oesophageal cancer: nationwide cohort study

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Abstract

Background: Accumulating evidence suggests a survival benefit after curative oesophageal cancer surgery in women compared with men. The aim of this study was to explore sex disparities in survival after surgery with curative intent in patients with oesophageal cancer.

Methods: This was a population-based cohort study, including all patients with oesophageal or gastric cancer who underwent surgery with a curative intent between 2006 and 2017 in Sweden. Female *versus* male mortality rate ratio (MRR) and excess mortality rate ratio (EMRR) were used as measures of survival. Two different parametric models were designed to account for potential confounders. Patients with gastric cancer were used as a comparison group as no differences in survival between sexes were expected among these patients.

Results: A total of 1301 patients underwent resection for oesophageal adenocarcinoma and 305 patients for oesophageal squamous cell carcinoma. Women had a lower EMRR (0.76, 95 per cent c.i. 0.58 to 1.01, $P = 0.056$; 0.52, 95 per cent c.i. 0.32 to 0.84, $P = 0.007$ respectively) in both histological subtypes. The effect was more profound in early clinical stages, in patients receiving neoadjuvant treatment, and without postoperative complications. No sex-related difference was observed in survival of patients with gastric cancer.

Conclusions: Women undergoing resection for oesophageal carcinoma have better survival compared with men.

Introduction

Oesophageal cancer is the ninth most common cancer diagnosis and the sixth most common cause of cancer-related death worldwide[1]. The incidence of oesophageal cancer is expected to rise and may cause an increased burden in the coming years due to an ageing population[2,3]. Although early diagnosis and better treatments have resulted in an improved prognosis, the 5-year survival rate remains low[3,4].

Sex differences in the incidence of oesophageal cancer for both major histological subtypes, oesophageal adenocarcinoma (OAC) and squamous cell carcinoma (OSCC), have been well described in many studies. Sex differences present substantial geographical variations that can be partly explained by different prevalence of risk factors, such as tobacco use and alcohol consumption[5–8]. Recent studies also suggest that sex may play a role in the prognosis after surgical treatment[9–11]. Surgical resection, together with chemotherapy, or chemoradiotherapy, is the treatment of choice for patients with non-metastatic locally advanced oesophageal cancer[12,13]. The 5-year survival rate after surgery is around 40 per cent for patients with OAC and OSCC in Sweden[14]. Patient characteristics such as age, smoking, co-morbidity, socioeconomic status, fitness, and performance status, as well as tumour-related factors such as tumour stage and biology are some of the factors that influence postoperative survival[15–20].

The aim of this study was to explore potential sex differences in survival after curative surgery for OAC and OSCC. Patients with gastric cancer were included as a comparison group, as no sex differences in survival after curative intent resection were expected in these patients.

Methods

Database and study design

A review was performed to identify patients who underwent oesophagectomy for OAC or OSCC or gastrectomy for cancer between 2006 and 2017 from a prospectively developed

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nationwide disease-specific quality registry, the National Register for Oesophageal and Gastric Cancer (NREV). All patients were followed from the date of surgery until death, emigration, or end of follow-up (15 March 2018), whichever occurred first. Only patients who underwent surgery with curative intent, (surgery alone, neoadjuvant chemo- or chemoradiotherapy followed by surgery, or surgery with perioperative chemotherapy), were included. Data on diagnostic workup, treatment, and follow-up were entered into the NREV electronically by trained doctors and nurses. NREV has a coverage of 95.5 per cent, compared with the National Cancer Registry, and an accuracy of 91.1 per cent of all entries in the data, according to a validation study conducted in 2016[21]. NREV was further linked to the Swedish registry of cause of death, Swedish National Inpatient Registry, and Total Population Registry to collect additional data and to perform censorship of follow-up. Detailed information regarding these registers is described elsewhere[22–24]. This study was approved by the Regional Ethical Review Board in Stockholm, Sweden (EPN Stockholm Dnr: 2016/1486-32 and 2013/596-31/3).

Tumour classification

NREV uses ICD-10 for the identification and categorization of tumour anatomical sites. Oesophageal cancer was defined as C15.0 to C16.0B or C16.0X, and gastric cancer was defined as C16.0C or C16.1 to C16.9. Patients without a definite histological identification were excluded from the analysis. Tumour stage was classified according to UICC TNM 8[25].

Clinical variables

Following a review of the literature[15,18–20], variables potentially affecting the prognosis of oesophageal cancer included age at time of surgery, Charlson co-morbidity index (0, 1, 2, and 3 or higher)[16], ASA score[26], tumour stage, marital status (married, unmarried, divorced, and widowed), educational level (9 years or less, 10–12 years, and more than 12 years), neoadjuvant treatment (none, chemotherapy, and chemoradiotherapy), and hospital volume (defined as mean value of oesophagectomies or gastrectomies in each hospital per year, stratified by tertiles)[17]. Data on

Table 1 Sex-specific main characteristics in groups of oesophageal adenocarcinoma and oesophageal squamous cell carcinoma

	Oesophageal adenocarcinoma		Oesophageal squamous cell carcinoma	
	Men ($n = 1098$)	Women ($n = 203$)	Men ($n = 199$)	Women ($n = 106$)
Age at operation (years)*	66.1 (9.0)	65.6 (10.8)	66.7 (8.8)	64.3 (10.4)
Education				
≤9 years	357 (33.0)	60 (30.2)	75 (38.7)	29 (28.4)
10–12 years	503 (46.5)	86 (43.2)	74 (38.1)	43 (42.1)
>12 years	221 (20.5)	53 (26.6)	45 (23.2)	30 (29.4)
Missing	17	4	5	4
Marital status				
Married	659 (60.0)	89 (43.8)	117 (58.8)	60 (56.6)
Unmarried	171 (15.6)	39 (19.2)	35 (17.6)	13 (12.3)
Divorced	199 (18.1)	35 (17.3)	41 (20.6)	13 (12.3)
Widowed	69 (6.3)	40 (19.7)	6 (3.0)	20 (18.9)
Anaesthetist score				
1	389 (36.0)	74 (37.2)	61 (30.8)	40 (38.1)
2	526 (48.7)	93 (46.7)	95 (48.0)	52 (48.5)
3	156 (14.5)	32 (16.1)	39 (19.7)	13 (12.4)
4	9 (0.8)	0	3 (1.5)	0
Missing	18	4	1	1
Clinical stage				
Stage 0	121 (11.1)	27 (13.3)	15 (7.6)	11 (10.4)
Stage I	292 (26.7)	70 (34.5)	47 (23.7)	31 (29.3)
Stage II	279 (25.5)	51 (25.1)	50 (25.3)	38 (35.8)
Stage III	387 (35.2)	50 (24.6)	83 (41.9)	25 (23.6)
Stage IV	16 (1.5)	5 (2.5)	3 (1.5)	1 (0.9)
Missing	3	0	1	0
Neoadjuvant treatment				
None	350 (33.5)	83 (43.0)	68 (35.1)	51 (50.0)
Chemotherapy	266 (25.5)	49 (25.4)	21 (10.8)	2 (2.0)
Chemoradiotherapy	429 (41.0)	61 (31.6)	105 (54.1)	49 (48.0)
Missing	53	10	5	4
Charlson co-morbidity index				
0	513 (46.7)	106 (52.2)	97 (48.7)	55 (51.9)
1	262 (23.9)	46 (22.7)	36 (18.1)	22 (20.7)
2	156 (14.2)	29 (14.3)	34 (17.1)	14 (13.2)
≥3	167 (15.2)	22 (10.8)	32 (16.1)	15 (14.2)
Hospital volume				
Low volume (first tertile)	298 (27.2)	68 (33.5)	46 (23.2)	22 (20.8)
Middle volume (second tertile)	373 (34.1)	55 (27.1)	54 (27.3)	35 (33.0)
High volume (third tertile)	423 (38.7)	80 (39.4)	98 (49.5)	49 (46.2)
Missing	4	0	1	0
Postoperative complications				
No	656 (59.7)	124 (61.1)	101 (50.8)	56 (52.8)
Yes	442 (40.3)	79 (38.9)	98 (49.2)	50 (47.2)

*Values are mean (s.d.).
Values in parentheses are percentages.

Table 2 Female *versus* male mortality rate ratio and excess mortality rate ratio at different follow-up times in each group

	Oesophageal adenocarcinoma: MRR model					
	Death number/person-years		Model 1*		Model 2†	
	Men	Women	MRR	P	MRR	P
1 year	270/961	40/181	0.80 (0.57, 1.12)	0.194	0.82 (0.57, 1.19)	0.297
5 years	324/1691	53/373	0.78 (0.61, 1.00)	0.046	0.78 (0.60, 1.01)	0.060
10 years	40/570	6/113	0.77 (0.61, 0.98)	0.032	0.77 (0.60, 1.00)	0.047
Overall	634/3249	99/671	0.77 (0.61, 0.98)	0.031	0.77 (0.60, 1.00)	0.047
	Oesophageal adenocarcinoma: EMRR model					
	Death number/person-years		Model 1*		Model 2†	
	Men	Women	EMRR	P	EMRR	P
1 year	270/961	40/181	0.78 (0.54, 1.13)	0.189	0.82 (0.55, 1.21)	0.312
5 years	324/1691	53/373	0.77 (0.59, 1.01)	0.058	0.77 (0.58, 1.03)	0.080
10 years	40/570	6/113	0.75 (0.58, 0.98)	0.032	0.76 (0.58, 1.01)	0.057
Overall	634/3249	99/671	0.75 (0.58, 0.98)	0.032	0.76 (0.58, 1.01)	0.056
	Oesophageal squamous cell carcinoma: MRR model					
	Death number/person-years		Model 1*		Model 2†	
	Men	Women	MRR	P	MRR	P
1 year	55/168	20/97	0.66 (0.39, 1.11)	0.116	0.92 (0.47, 1.78)	0.794
5 years	69/269	24/203	0.53 (0.36, 0.78)	0.001	0.51 (0.32, 0.81)	0.004
10 years	11/88	4/83	0.54 (0.37, 0.79)	0.002	0.52 (0.33, 0.81)	0.004
Overall	135/530	48/387	0.54 (0.37, 0.79)	0.002	0.51 (0.33, 0.81)	0.004
	Oesophageal squamous cell carcinoma: EMRR model					
	Death number/person-years		Model 1*		Model 2†	
	Men	Women	EMRR	P	EMRR	P
1 year	55/168	20/97	0.66 (0.38, 1.15)	0.146	0.98 (0.49, 1.99)	0.963
5 years	69/269	24/203	0.52 (0.34, 0.78)	0.002	0.50 (0.30, 0.82)	0.006
10 years	11/88	4/83	0.53 (0.35, 0.79)	0.002	0.52 (0.32, 0.84)	0.007
Overall	135/530	48/387	0.53 (0.35, 0.79)	0.002	0.52 (0.32, 0.84)	0.007

Values in parentheses are 95 per cent confidence intervals.
*Adjusted for age.
†Adjusted for age, co-morbidity, ASA level, clinical stage, neoadjuvant treatment, marital status, education level, and hospital volume. MRR, male mortality rate ratio; EMRR, excess mortality rate ratio.

postoperative complications rate, defined as any complication occurring within 30 days after surgery, were also collected.

Outcomes

Outcomes of interest in the study included mortality rate and excess mortality rate at 1 year, 5 years, 10 years, and across the whole follow-up interval.

Statistical methods

Female *versus* male mortality (MRR) and excess mortality rate ratio (EMRR), absolute differences in mortality, and excess mortality rate were used to study survival.

Excess mortality rate was defined as the difference between the observed mortality rate in the study cohort and the expected mortality rate of the Swedish population in the same interval retrieved from the Human Mortality Database of Sweden (http://www.mortality.org), matched by age, sex, and calendar year. Excess mortality rate was used as a surrogate measure of cancer-specific mortality as it does not require any classification of cause of death that in everyday practice might be inaccurate, especially within 1 month of surgery[27,28].

Flexible parametric models were applied to compute MRRs and EMRRs in each group with the stpm2 Stata procedure. With the sex coefficient set to be time dependent, the method allowed for a flexible estimation of baseline hazard, enabling the prediction of mortality rate as a function of follow-up time with a specific pattern of covariates[29,30]. Two different models were designed. Model 1 included age at the time of surgery, whereas model 2 included age at the time of surgery, Charlson co-morbidity index, ASA score, tumour stage, marital status, education level, and hospital volume. Each model was evaluated at 1 year, 5 years, 10 years, and across the whole follow-up time, in each type of cancer. To identify potential confounders, analyses were also stratified by tumour stage, neoadjuvant treatment, and postoperative complications. Degrees of freedom were determined by the Akaike information criterion, Bayesian information criterion, and likelihood ratio test.

Sex-specific mortality rates and excess mortality rates were predicted based on model 2 with the standsurv Stata postestimation command of the stpm2 procedure[31]. Individual calculation of mortality and excess mortality rates were made by setting covariates as observational values and sex was fixed to be male and then female in the model, separately, whatever the

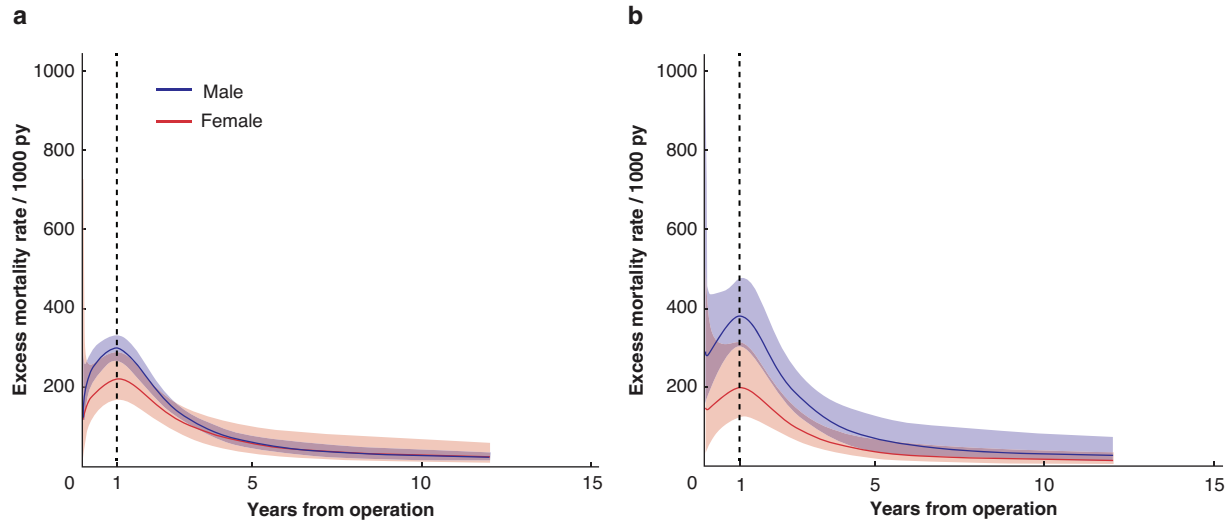

Fig. 1 Sex-specific excess mortality rates per 1000 person-years with corresponding 95 per cent confidence intervals in each group, adjusting for age, co-morbidity, ASA level, clinical stage, neoadjuvant treatment, marital status, education level, and hospital volume

a Oesophageal adenocarcinoma. **b** Oesophageal squamous cell carcinoma.

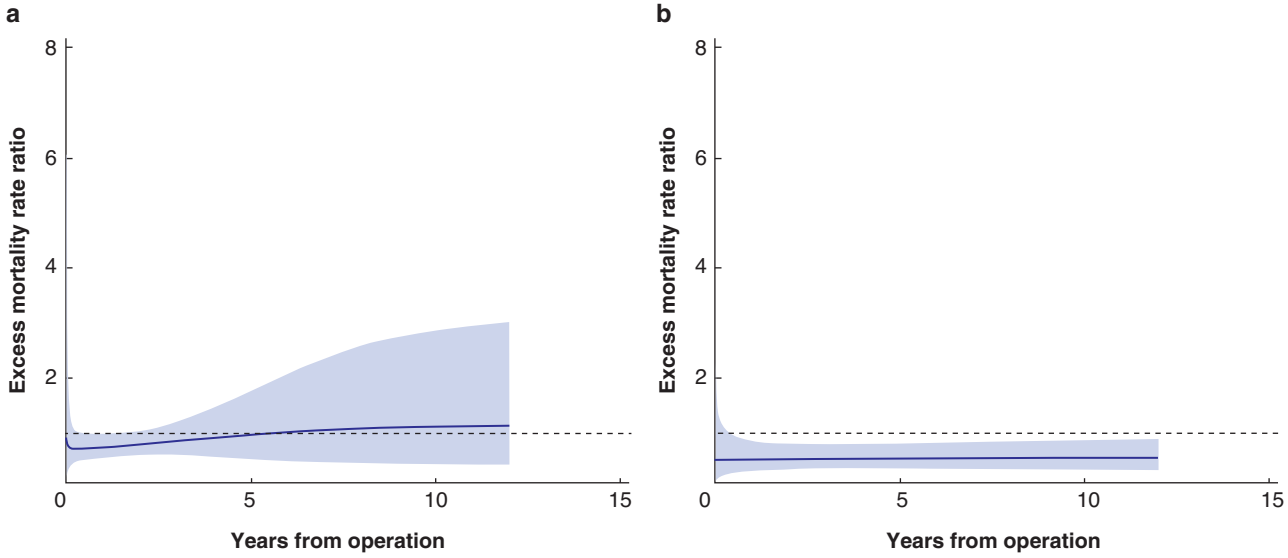

Fig. 2 Female *versus* male excess mortality rate ratios with corresponding 95 per cent confidence intervals in each group, adjusting for age, co-morbidity, ASA level, clinical stage, neoadjuvant treatment, marital status, education level, and hospital volume

a Oesophageal adenocarcinoma. **b** Oesophageal squamous cell carcinoma.

actual sex was. Individual estimates were then averaged over the whole population with sex set to male or female separately. Thereafter, absolute differences and ratios of mortality rates and excess mortality rates between men and women were calculated and plotted over follow-up time to describe time trends.

As a sensitivity analysis, the results of the flexible parametric models were compared with a Cox regression model. All the analyses were performed on an intention-to-treat basis. All analyses were carried out with Stata 15.0 (StataCorp, College Station, Texas, USA). A P value <0.05 was considered statistically significant.

Results

A total of 1301 patients with OAC, 1098 men (84.4 per cent) and 203 women (15.6 per cent); 305 patients with OSCC, 199 men (65.2 per cent) and 106 women (34.8 per cent); and 1597 patients with gastric cancer, 940 men (58.9 per cent) and 657 women (41.1 per cent) were included in the study. Patient characteristics according to sex and histological subtypes are reported in *Table* 1. Patient characteristics of gastric adenocarcinoma are shown in *Table S1*.

Female *versus* male MRRs and EMRRs at different time points after surgery according to models 1 and 2 are presented in *Table* 2. In patients with OAC, women had a risk reduction of mortality and excess mortality rate slightly greater than 20 per cent overall and at 10 years after surgery according to model 1 (overall and at 10 years in model 1, MRR 0.77 (0.61–0.98); EMRR 0.75 (0.58–0.98)). No statistically significant differences in female *versus* male MRRs or EMRRs were found at any other time point and/or according to model 2. In patients with OSSC, women had almost half the mortality and excess mortality

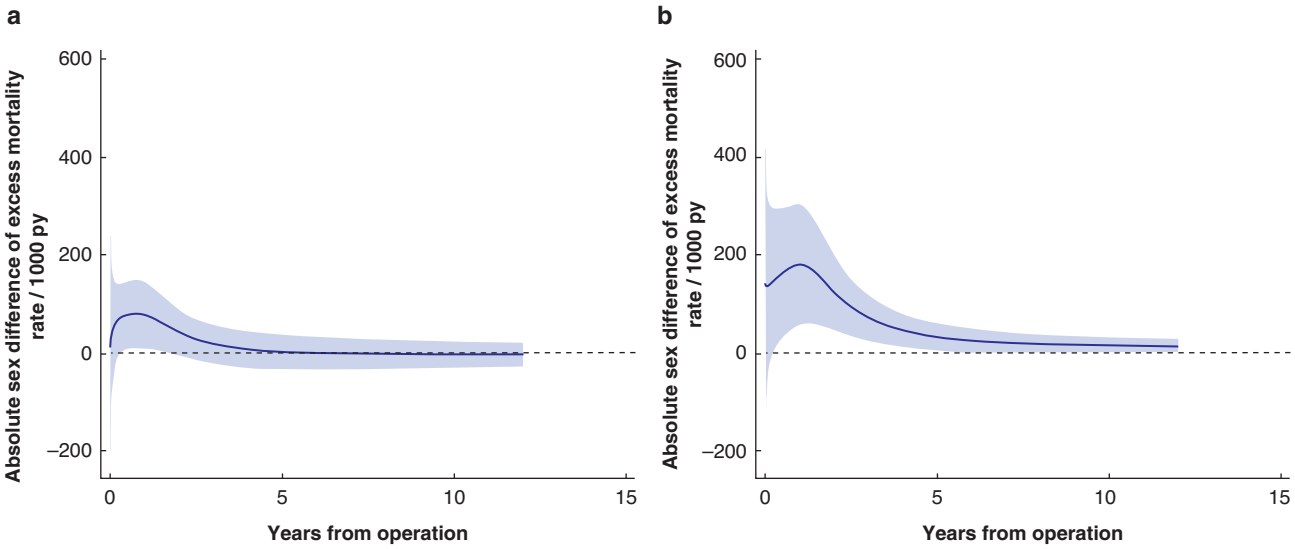

Fig. 3 Absolute difference of excess mortality rates with corresponding 95 per cent confidence intervals in each group, controlling for age, co-morbidity, ASA level, clinical stage, neoadjuvant treatment, marital status, education level, and hospital volume

a Oesophageal adenocarcinoma. **b** Oesophageal squamous cell carcinoma.

Table 3 Female *versus* male mortality rate ratios, excess mortality rate ratios stratified by clinical stages in each group

Oesophageal adenocarcinoma (total number/death number)	MRR Model 1*	MRR Model 2†	EMRR Model 1*	EMRR Model 2†
Stage 0–I				
Men ($n = 413/212$)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Women ($n = 97/40$)	0.79 (0.55, 1.15)	0.65 (0.43, 0.98)	0.79 (0.52, 1.22)	0.59 (0.36, 0.97)
Stage II				
Men ($n = 279/160$)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Women (51/27)	0.82 (0.51, 1.32)	0.86 (0.52, 1.42)	0.81 (0.48, 1.37)	0.88 (0.52, 1.50)
Stage III–IV				
Men ($n = 403/259$)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Women (55/32)	0.83 (0.54, 1.28)	0.79 (0.51, 1.22)	0.82 (0.51, 1.31)	0.80 (0.51, 1.26)
Oesophageal squamous cell carcinoma (total number/death number)	**MRR Model 1***	**MRR Model 2†**	**EMRR Model 1***	**EMRR Model 2†**
Stage 0–I				
Men (62/45)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Women (42/16)	0.37 (0.19, 0.75)	0.28 (0.11, 0.68)	0.34 (0.15, 0.68)	0.29 (0.11, 0.75)
Stage II				
Men (50/33)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Women (38/16)	0.59 (0.30, 1.15)	0.65 (0.29, 1.46)	0.59 (0.28, 1.23)	0.66 (0.26, 1.64)
Stage III–IV				
Men (86/56)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Women (26/16)	0.92 (0.48, 1.77)	0.65 (0.27, 1.52)	0.92 (0.47, 1.82)	0.62 (0.25, 1.56)

Values in parentheses are 95 per cent confidence intervals.
*Adjusted for age.
†Adjusted for age, co-morbidity, ASA level, neoadjuvant treatment, marital status, education level, and hospital volume. MRR, male mortality rate ratio; EMRR, excess mortality rate ratio.

rate compared with men overall, at 5 and 10 years after surgery according to both models (overall model 1, MRR 0.54 (0.37–0.79); EMRR 0.53 (0.35–0.79); overall model 2, MRR 0.51 (0.33–0.81); EMRR 0.52 (0.32–0.84)). Time trends for excess mortality rates in the OAC and OSCC groups, adjusting for potential covariates according to model 2, are shown in *Fig. 1*. Time trends for mortality rates, adjusting for potential covariates according to model 2, are shown in *Fig. S1*. Time trends for female *versus* male EMRRs in OAC and OSCC groups, adjusting for potential covariates according to model 2, are shown in *Fig. 2*. Time trends for female *versus* male MRRs, adjusting for potential covariates according to model 2, are shown in *Fig S2*.

Time trends for absolute differences in excess mortality rates according to histological subtype in oesophageal cancer are shown in *Fig. 3*. Time trends for absolute differences in mortality rates are shown in *Fig S3*.

In patients with gastric cancer, there was no difference in mortality and excess mortality rates between men and women at any time point after surgery according to both models (*Table S2*). Time trends for mortality and excess mortality rates, adjusting for potential covariates according to model 2, are

Table 4 Female *versus* male mortality rate ratios, excess mortality rate ratios stratified by perioperative neoadjuvant treatment in each group

Oesophageal adenocarcinoma (total number/death number)	MRR Model 1*	MRR Model 2†	EMRR Model 1*	EMRR Model 2†
Without neoadjuvant treatment				
Men ($n = 350/226$)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Women ($n = 83/47$)	0.97 (0.69, 1.38)	0.99 (0.68, 1.43)	1.01 (0.68, 1.49)	1.05 (0.69, 1.59)
With neoadjuvant treatment				
Men ($n = 695/391$)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Women (110/50)	0.67 (0.47, 0.95)	0.63 (0.43, 0.90)	0.66 (0.45, 0.96)	0.62 (0.42, 0.92)
Oesophageal squamous cell carcinoma (total number/death number)	**MRR Model 1***	**MRR Model 2†**	**EMRR Model 1***	**EMRR Model 2†**
Without neoadjuvant treatment				
Men (68/58)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Women (51/30)	0.64 (0.38, 1.07)	0.67 (0.36, 1.26)	0.63 (0.36, 1.11)	0.69 (0.35, 1.37)
With neoadjuvant treatment				
Men (126/75)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Women (51/17)	0.37 (0.19, 0.72)	0.32 (0.14, 0.70)	0.36 (0.18, 0.73)	0.31 (0.13, 0.71)

Values in parentheses are 95 per cent confidence intervals.
*Adjusted for age.
†Adjusted for age, co-morbidity, ASA level, clinical stage, marital status, education level, and hospital volume. MRR, male mortality rate ratio; EMRR, excess mortality rate ratio.

Table 5 Female *versus* male mortality rate ratios, excess mortality rate ratios stratified by postoperative complications in each group

Oesophageal adenocarcinoma (total number/death number)	MRR Model 1*	MRR Model 2†	EMRR Model *	EMRR Model 2†
No postoperative complications				
Men (656/359)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Women (124/58)	0.69 (0.50, 0.96)	0.66 (0.46, 0.94)	0.66 (0.45, 0.99)	0.64 (0.42, 0.96)
Any postoperative complications				
Men (442/275)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Women (79/41)	0.87 (0.61, 1.26)	0.89 (0.61, 1.32)	0.88 (0.60, 1.30)	0.91 (0.60, 1.38)
Oesophageal squamous cell carcinoma (total number/death number)	**MRR Model 1***	**MRR Model 2†**	**EMRR Model 1***	**EMRR Model 2†**
No postoperative complications				
Men (101/62)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Women (56/20)	0.41 (0.22, 0.76)	0.28 (0.14, 0.58)	0.41 (0.21, 0.81)	0.28 (0.13, 0.63)
Any postoperative complications				
Men (98/73)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Women (50/28)	0.61 (0.36, 1.03)	0.50 (0.26, 0.96)	0.61 (0.35, 1.05)	0.49 (0.25, 0.98)

Values in parentheses are 95 per cent confidence intervals.
*Adjusted for age.
†Adjusted for age, co-morbidity, ASA level, clinical stage, marital status, education level, and hospital volume. MRR, male mortality rate ratio; EMRR, excess mortality rate ratio.

shown in *Fig. S4*. Time trends for female *versus* male MRRs and EMRRs, adjusting for potential covariates according to model 2, are shown in *Fig. S5*. Absolute difference of mortality rates and excess mortality rates are shown in *Fig S6*.

Stratified analyses by tumour stage, neoadjuvant therapy, and postoperative complications in patients with oesophageal cancer are shown in *Tables* 3–5 respectively. A reduction in mortality and excess mortality rate was observed in women with oesophageal cancer in stage I, who underwent neoadjuvant therapy and did not develop postoperative complications, regardless of histological subtype. In patients with oesophageal cancer with a more advanced disease, who did not receive neoadjuvant therapy but developed postoperative complications, no differences in mortality and excess mortality rate were observed between sexes.

Stratified analyses by tumour stage, neoadjuvant therapy, and postoperative complications in patients with gastric cancer are shown in *Tables S3–S5* respectively.

In the sensitivity analysis, hazard ratios in each group were calculated with a Cox regression model with time after surgery and age as the time scale; the results did not substantially differ from the main analyses, and results are shown in *Tables S6 and S7*.

Discussion

In women undergoing oesophageal cancer surgery a survival benefit was observed compared with men. The survival benefit was greater in patients with OSCC compared with patients with OAC and persisted after stratified analyses in patients with an early tumour stage, who underwent neoadjuvant therapy, and did not develop postoperative complications.

Data available in the literature are conflicting. Studies from Japan and Sweden showed a survival benefit in women compared with men mostly in patients with OSCC[9,10], while a study from the US found no sex difference in overall survival in

patients with oesophageal cancer, but, after adjusting for a limited number of confounders, women had a slightly higher mortality risk in tumour stage II/III[11].

A potential explanation for the sex difference in survival after oesophageal cancer surgery is that oestrogen might play a protective role in the development and survival of oesophageal cancer[32,33], although the specific biological mechanism is unknown. Studies stratified by age did not show a better survival in younger women with high levels of sex hormones[9], which does not support a protective effect of oestrogen. Other explanations for the difference between men and women could involve socioeconomic status, lifestyle, alcohol consumption, tobacco use, and obesity as key factors for the prognosis of oesophageal cancer[7,34]. Abdominal obesity, which is prevalent in men, is suggested to be an independent risk factor for OAC and partly explained the male dominance in the incidence of OAC[35,36]; however, the association between obesity and the postoperative survival of OAC is controversial and the mechanism remains largely unclear. Meta-analysis showed that obese patients tend to be associated with surgical complications such as anastomotic leak, yet have a better 5-year survival[37,38]. On the other hand, obesity may bring difficulties to the accurate cancer diagnosis, lack of ideal calculation of chemotherapy doses, and complex postsurgical complications, which may lead to poorer treatment outcomes[39]. Additionally, sex differences in survival after oesophageal cancer treatment may also be related to administration of neoadjuvant therapy. Sex-related difference in the pharmacokinetics and pharmacodynamics might affect the exposure, clearance, efficacy, toxicity, and adverse effects of chemotherapy, thus women might be overtreated and men undertreated[40,41]. Women that received neoadjuvant chemoradiotherapy have also shown a better response to treatment and a lower risk for tumour recurrence[42]. It has also been shown among patients with locoregional disease treated with oesophagectomy that women received neoadjuvant therapy less frequently, had more positive margins, and a worse overall survival than men[11].

In the present study, high completeness, precision, and correctness in follow-up information were reached combining and cross-matching data from several nationwide comprehensive healthcare registers[43,44]. Some limitations, however, need to be mentioned. Despite being a population-based study, further subgroup analysis was not feasible given the low incidence of oesophageal cancer in women. To perform excess mortality analysis sex, age, and calendar year only were used as matching factors. Detailed information about other potential confounding factors, such as dietary factors, tobacco use, alcohol consumption, and BMI were not available. Data on postoperative complications lacked detail on severity, therefore, conclusions that can be drawn on this subgroup of patients are limited.

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Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

Data cannot be shared publicly because of regulations in the Swedish Data Protection Act (2018:218; 2019; 219) and Ethical Review Act (2003:460). Data are available from the holder of the NREV register (J. Johansson; Jan.johansson@med.lu.se) for researchers who meet the criteria for access to confidential data.

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