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ORIGINAL ARTICLE

Confounders other than comorbidity explain survival differences in Danish and Swedish ovarian cancer patients – a comparative cohort study

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ABSTRACT

Objective: Danish ovarian cancer (OC) patients have previously been found to have worse prognosis than Swedish patients, and comorbidity has been suggested as a possible explanation for this survival difference. We aimed to investigate the prognostic impact of comorbidity in surgically treated OC patients in Denmark and Sweden.

Methods: This comparative cohort study was based on data from 3118 surgically treated OC patients diagnosed in 2012–2015. The Swedish subcohort ($n = 1472$) was identified through the Swedish National Quality Register of Gynecological Surgery, whereas the Danish subcohort ($n = 1646$) originated from the Danish Gynecological Cancer Database. The clinical databases have high coverage and similar variables included. Comorbidity was classified according to the Ovarian Cancer Comorbidity Index and overall survival was the primary outcome. Data were analyzed using Kaplan Meier and Cox regression analyses. Multiple imputation was used to handle missing data.

Results: We found comparable frequencies of the following comorbidities: Hypertension, diabetes and 'Any comorbidity'. Arteriosclerotic cardiac disease and chronic pulmonary disease were more common among Swedish patients.

Univariable survival analysis revealed a significant better prognosis for Swedish than for Danish patients (HR 0.84 [95% CI 0.74–0.95], $p < .01$). In adjusted multivariable analysis, Swedish patients had nonsignificant better prognosis compared to Danish patients (HR 0.91 [95% CI 0.80–1.04], $p = .16$). Comorbidity was associated with survival ($p = .02$) but comorbidity did not explain the survival difference between the two countries.

Conclusions: Danish OC patients have a poorer prognosis than patients in Sweden but the difference in survival seems to be explained by other factors than comorbidity.

Abbreviations: NICP: National Integrated Cancer Pathways; CI: Confidence interval; GynOp: Swedish National Quality Register of Gynecological Surgery; DGCD: Danish Gynecological Cancer Database; OCCI: Ovarian Comorbidity Cancer Index; FIGO: International Federation of Gynecology and Obstetrics; NACT: Neoadjuvant chemotherapy; BMI: Body Mass Index; OS: Overall survival; MI: Multiple Imputation; MAR: Missing At Random; HR: Hazard Ratio; CI: Confidence Interval

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Introduction

Denmark and Sweden are Scandinavian countries of comparable populations and with similar, mainly tax-financed, health care systems [1–3]. However, a remarkably large difference in cancer survival between populations in the two countries exists and this fact continues to marvel professional health care providers, researchers and decision makers [4]. Since comparative studies of cancer survival began, Denmark has repeatedly been identified as the Nordic country with the poorest survival across cancer sites, whereas Sweden usually ranks first in regard to cancer survival [4,5]. The continuous bottom ranking compared to neighboring countries has within the last 15 years led to extensive political health care related initiatives in Denmark: Cancer treatment was centralized; the National Integrated Cancer Pathways (NICP) (i.e., fast track diagnostic work-up for patients with symptoms and/or clinical findings suspicious of malignancy) were implemented and clinical quality databases were established [6,7]. This has had a pronounced positive effect on Danish ovarian cancer survival, but ovarian cancer mortality in Denmark is still reported higher compared to Sweden. Thus, five year relative survival rates for Danish ovarian cancer patients diagnosed 2010–2014 were 40% (95% confidence interval (CI) 38–42%) compared to 48% (95% CI 46–49%) in Swedish patients [8]. The reasons for the observed survival differences remain unclear, but differences in comorbidity prevalence and

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Supplemental data for this article can be accessed here.

severity have been suggested as a possible explanation. Several studies have demonstrated that the presence of comorbidity is associated with poorer prognosis in ovarian cancer [9–13]. As Danish women for example are known to be more frequent smokers as well as smoke larger number of cigarettes per day and have higher alcohol consumption than women living in Sweden, life-style related comorbidity may be more common among Danish ovarian cancer patients [2,14–16]. The aim of this study was to study comorbidity among ovarian cancer patients in Denmark and Sweden and to explore and compare the impact of comorbidity on prognosis in these two otherwise similar Scandinavian countries.

Material and methods

Study design and setting

This is a register-based comparative cohort study based on data from Denmark and Sweden. Measured by population size, Denmark is the smallest country (5.7 mill), whereas Sweden with a population of 9.8 mill inhabitants is the largest country in Scandinavia. Both countries have tax-financed health care systems with only a small fraction of health care services paid out-of-pocket.

Data sources and study populations

The Nordic countries are known to have registers of high coverage and quality. Further, registers are quite similar why comparative studies can be conducted without major difficulties [17]. Data for this study were obtained from the following sources:

The Swedish study population was obtained via the Swedish National Quality Register for Gynecological Surgery (GynOp). Gynecological clinics in four out of six regions in Sweden report to GynOp and the register is thereby covering 5.03 million people or 52% of the Swedish population [18]. Since only few patients are referred outside of their region, GynOp is considered to have full (>95%) population coverage in the regions reporting to the register. Since 2004 GynOp includes all major gynecological operations and patients are included in the register when surgery is scheduled. Preoperative health questionnaires including comorbidity, earlier surgery, medication etc. are answered by the patients, the doctor reports data to the registry at admission, surgery and discharge and when the histopathology results arrive.

We identified 2288 cases of surgery in women 15 years or above registered in the time period 1 January 2012 till 31 December 2015 with a preoperative diagnosis of ovarian, peritoneal or fallopian tube cancer. We excluded 163 cases due to duplicate registration and another 551 cases were excluded as the final pathology report showed nonovarian cancer or borderline pathology. A total of 102 cases received surgical treatment for a recurrence and these were excluded as well. Follow-up was obtained by linking personal numbers with data from the Swedish population registry. No patients were lost to follow-up. The Swedish subcohort therefore consisted of 1472 ovarian cancer patients and follow-up ended on 15 December 2016 (Figure 1).

Patients in the Danish subcohort were identified through the Danish Gynecological Cancer Database (DGCD). This is a nationwide clinical database containing detailed information on gynecological cancers diagnosed in Denmark since 2005 [19]. Reporting data to the database is mandatory and coverage is 97% according to recent annual report [20]. A total of 1964 patients were registered in DGCD with a confirmed primary diagnosis of ovarian, peritoneal or fallopian tube cancer from 1 January 2012 till 31 December 2015 (borderline tumors excluded). We excluded 20 cases lost to follow-up, and three cases were excluded due to age <15 years. As explained above the GynOp only contains information on surgically treated ovarian cancer patients as opposed to the DGCD which contains information on all ovarian cancer patients regardless of treatment. To obtain as comparable cohorts as possible, we have excluded 295 Danish patients who did not receive any surgical treatment or a palliative/diagnostic procedure such as thoracocentesis or laparocentesis only. A total of 1646 Danish patients were included in the study and follow-up ended on 17 May 2017 (Figure 1).

Comorbidity

GynOp and DGCD are both clinical databases and information on comorbidity is registered by clinicians upon admission to the gynecologic department. Information is based on patients self-reports and/or previous notes in the patient files. Comorbidities are registered by name (ex. 'arteriosclerotic cardiac disease') in the databases (i.e., no ICD-10 codes are registered).

We used a modified version of the recently developed Ovarian Cancer Comorbidity Index (OCCI) for the classification of comorbidity [21] (Table 2). The OCCI score is an age-stratified linear predictor of five-year overall survival (OS), and the calculation of the original OCCI score is based on the presence of the following five comorbidities: 'Arteriosclerotic cardiac disease', 'Chronic obstructive pulmonary disease', 'Hypertension', 'Dementia' and 'Diabetes'. As accounted for in the notes of Table 2, several variables for cardiac and pulmonary comorbidity exist in the GynOp and the DGCD, why some were combined for the calculation of the OCCI score. Further, we had to leave out 'dementia' from the comorbidity score calculation as no valid information on this comorbidity existed in the GynOp. The index score was calculated as the sum of the regression coefficients for each of the four comorbidities as described in the original paper [21].

Covariates

Cancer stage was categorized according to the International Federation of Gynecology and Obstetrics (FIGO) 2013 stage classification, and the variable Histology was categorized as: 'Serous', 'Mucinous', 'Endometrioid', 'Clear cell', 'Sarcoma' and 'Rare types'. Residual tumor was divided into 'No macroscopic residual' when the surgeon had stated that no visible tumor was left at the end of surgery and 'Macroscopic residual tumor' if visible tumor was left. Choice of primary treatment

was categorized as 'Primary surgery' or 'NACT' (neoadjuvant chemotherapy followed by interval debulking surgery).

Nutritional status was assessed with the Body Mass Index (BMI) and the World Health Organization definition of BMI was used to categorize this variable [22]. The variable Smoking habits was classified as 'Smoker', 'Ex-smoker' and 'Never smoked'.

Outcome measures

Our primary outcome was overall survival (OS). Survival time was defined as time from ovarian cancer diagnosis till death from any cause or till the end of follow-up (censored). Swedish patients had a follow-up of maximum 59 months whereas Danish patients had a slightly longer follow-up of a maximum of 66 months.

Statistical analyses

Pearson Chi^2-test (for categorical variables) and Wilcoxon Rank test (for quantitative variables) were used to compare descriptive statistics by country of origin. Survival probabilities were estimated using the Kaplan–Meier method and compared by the log-rank. Multivariable Cox regression analyses were further performed to assess the difference between the two countries adjusted for covariates (confounders). To assess the proportional hazards assumption, the log hazard ratios were modeled as a function of time using spline functions and time-varying effects were assessed by joint Wald tests [23]. Multiple Imputation (MI) of missing data was performed taking the time-varying effects of some of the covariates into account [24]. Missing values of covariates were assumed to be Missing At Random (MAR) conditional on observed covariates and outcome [23]. The imputation procedure was based on observed outcome and covariates (country, age, comorbidity, primary treatment, residual tumor, stage, histology and nutritional status) included in the fully adjusted Cox regression model. All covariates were allowed to have time-varying effects in the imputation model. Ten multiply imputed data sets were generated and results were combined using Rubin's rules [25]. Several multivariable Cox regression analyses were fitted to the data set with complete values as well as the imputed data: (1) each covariate adjusted for age only, all effects assumed to be time-independent (Table 3), (2) multivariable Cox regression models assuming all effects to be time-independent (Table 3) and (3) multivariable Cox regression models allowing only confounders with time-independent effects to be time-independent (Table 4). The model using approach 3) (Table 4) based on all covariates is considered the final model, whereas the models assuming all effects to be time-independent are included only to give a simple description of the associations between covariates and survival. For these models, the reported hazard ratios (HR) should be interpreted as average effects over time. Several models with different groups of covariates were fitted to assess the confounding impact of the covariates on the HR comparing the two countries.

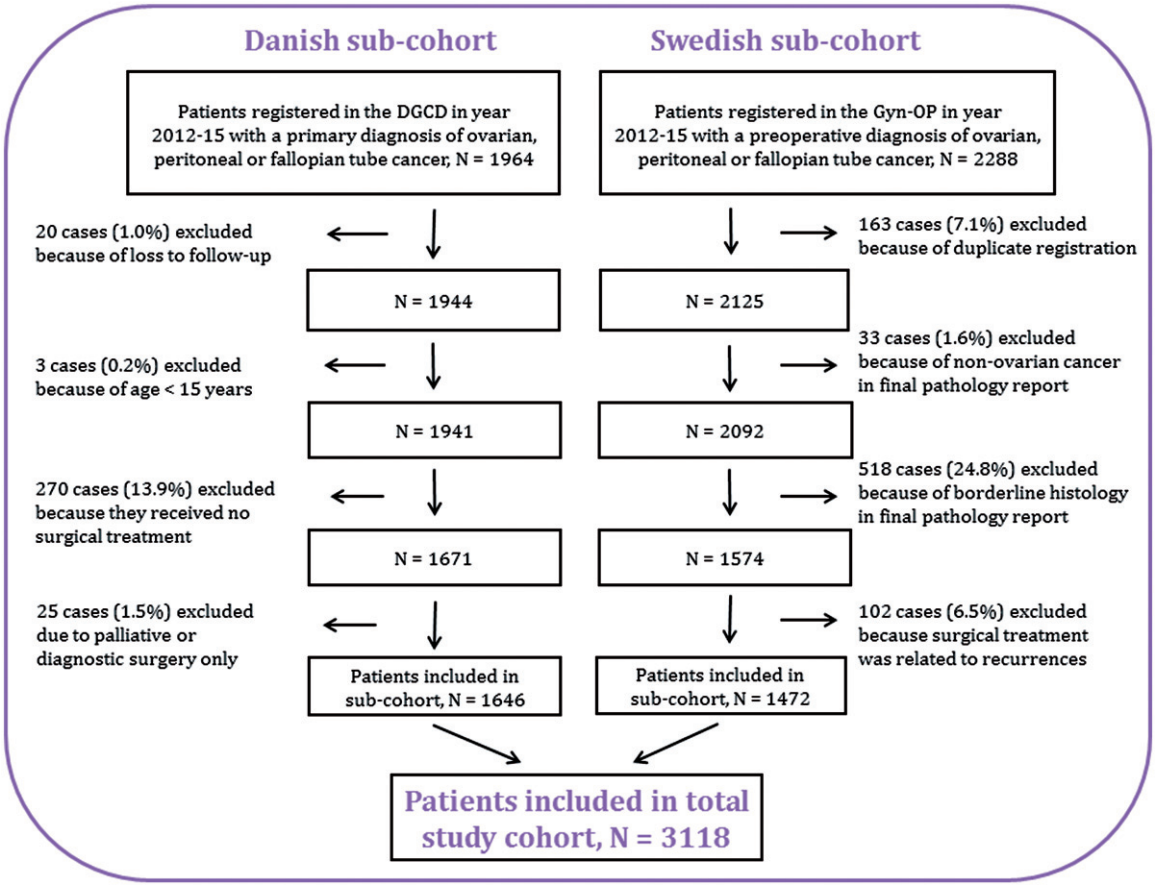

Figure 1. Flow chart describing the study population.

Significance was defined as $p < .05$ and estimates are presented with 95% confidence intervals (CI).

Data were analyzed using SPSS statistical software version 22 (IBM Corp., Armonk, NY), SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.4.0.

Results

General patient characteristics are shown in Table 1. A total of 37.7% of Danish patients were diagnosed with localized disease (stage I or II) compared to 33.4% of Swedish patients. Advanced disease (stage III–IV) was diagnosed in 66.6% of Swedish patients and 62.3% of Danish patients.

Table 1. Baseline characteristics of the study population, $n = 3118$.

Characteristics	Denmark, $n = 1646$ *n* (%)[a]	Sweden, $n = 1472$ *n* (%)[a]	*p* value[b]
Stage			
I	483 (30.1)	284 (26.6)	<.001
II	122 (7.6)	73 (6.8)	
III	715 (44.6)	596 (55.9)	
IV	282 (17.6)	114 (10.7)	
Missing data, *n*	44	405	
Histology			<.001
Serous adenocarcinoma	1114 (68.4)	611 (74.0)	
Mucinous adenocarcinoma	119 (7.3)	57 (6.9)	
Endometrioid adenocarcinoma	124 (7.6)	68 (8.2)	
Clear cell adenocarcinoma	93 (5.7)	44 (5.3)	
Sarcoma	68 (4.2)	10 (1.2)	
Rare types	111 (6.8)	36 (4.4)	
Missing data, *n*	17	646	
Residual tumor			.006
No macroscopic residual	1114 (69.4)	852 (64.6)	
Macroscopic residual tumor	491 (30.6)	467 (35.4)	
Missing data, *n*	41	153	
Primary treatment			<.001
Primary surgery	1156 (70.3)	1213 (83.0)	
NACT	489 (29.7)	248 (17.0)	
Missing data, *n*	1	11	
Age			.950
15–44 years	116 (7.0)	91 (6.2)	
45–54 years	241 (14.6)	215 (14.6)	
55–64 years	409 (24.8)	389 (26.4)	
65–74 years	560 (34.0)	501 (34.0)	
≥75 years	320 (19.4)	276 (18.8)	
Median (interquartile range), years	65 (56–73)	65 (56–72)	
OCCI score[c]			.088
OCCI <0	330 (20.1)	289 (19.6)	
OCCI =0	1083 (65.8)	931 (63.3)	
OCCI >0	233 (14.2)	252 (17.1)	
Median (min, max)	0 (−0.29–1.02)	0 (−0.29–1.42)	
Nutritional status			<.001
Underweight: BMI <18.5	89 (5.7)	26 (2.4)	
Normal weight: 18.5 ≥ BMI <25	760 (49.1)	511 (46.3)	
Overweight: 25 ≥ BMI <30	452 (29.2)	365 (33.1)	
Obesity: 30 ≥ BMI <35	167 (10.8)	134 (12.2)	
Severe obesity (BMI ≥35)	80 (5.2)	67 (6.1)	
Missing data, *n*	98	369	
Smoking habits			<.001
Never smoked	878 (55.5)	612 (54.4)	
Ex-smoker	444 (28.0)	403 (35.9)	
Smoker	261 (16.5)	109 (9.7)	
Missing data, *n*	63	348	

[a]Percentage of subcohort with registered values on the variable
[b]Chi^2-test was used for categorical variables and Wilcoxon Rank-sum test was used for quantitative variables.
[c]The Ovarian Cancer Comorbidity index (OCCI) is calculated as a linear age-stratified predictor of overall survival.

Total macroscopic debulking was achieved in 69.4% of Danish patients compared to 64.6% in Swedish patients ($p = .006$).

A significant difference in choice of primary treatment (primary surgery vs. NACT) was observed between the two countries as 70.3% Danish patients were treated with primary debulking surgery compared to 83.0% of Swedish patients ($p < .001$).

In both cohorts, serous adenocarcinoma was the most common histological subtype followed by endometrioid, mucinous and clear cell adenocarcinomas in that order.

Median age was 65 in both countries ($p = .95$). A total of 45.2% of Danish patients were overweight/obese (BMI ≥25) compared to 51.5% of Swedish patients ($p < .001$). Correspondingly, underweight (BMI <18.5) was observed more often in Danish patients (5.7% vs. 2.4%). A higher frequency of current smokers was observed among Danish patients (16.5% vs. 9.7%) whereas a larger fraction of Swedish patients were ex-smokers (35.9% vs. 28.0%) ($p < .001$).

The missing data pattern is presented in more detail in supplementary material S1.

Information on registered comorbidity is presented in Table 2. We observed comparable frequencies of hypertension and diabetes, and a similar proportion of Danish (52.9%) and Swedish (53.5%) patients were categorized as having 'Any comorbidity' ($p = .73$). In contrast, arteriosclerotic cardiac disease ($p < .01$) and pulmonary disease ($p = .02$) were more common among Swedish patients (Table 2). As a result, the linear OCCI score was slightly higher for Swedish patients than for Danish patients but the difference was not statistically significant ($p = .09$) (Table 1).

Survival analyses

Comparison of Kaplan–Meier curves for OS revealed a significant difference between Swedish and Danish patients (log-rank test: $p < .001$) (Figure 2).

The association between survival, country and comorbidity was explored further in multivariable Cox regression analyses using multiply imputed data and complete cases (Tables 3–5).

Table 2. The prevalence of comorbidity by country.

Comorbidity	Denmark, *N* (%)	Sweden, *N* (%)	*p* value[a]
Hypertension	447 (27.2)	419 (28.5)	.42
Arteriosclerotic cardiac disease	55 (3.3)[b]	78 (5.3)[c]	<.01
Chronic pulmonary disease	105 (6.4)[d]	125 (8.5)[e]	.02
Diabetes (insulin – and non-insulin-dependent)	85 (5.2)	90 (6.1)	.25
Any comorbidity registered	871 (52.9)[f]	788 (53.5)[g]	.73

[a]Chi^2-test was used for assessment of the association between comorbidity and country of treatment.
[b]DGCD variables 'Myocardial infarction' and 'Coronary arteriosclerosis' were used for this category.
[c]GynOp variables 'Congestive heart failure', 'Myocardial infarction', 'Angina pectoris' and 'Other cardiac disease' were used for this category.
[d]DGCD variables 'Chronic obstructive pulmonary disease' and 'Asthma' were used for this category.
[e]GynOp variables 'Chronic cough', 'Wheezing' and 'Other pulmonary disease' were used for this category.
[f]Registration of at least one out of 22 comorbidity variables in the DGCD.
[g]Registration of at least one out of 16 comorbidity variables in the GynOp.

Stage and residual tumor were confirmed as prognostic factors ($p < .001$) and primary surgery was associated to significantly better survival compared to NACT ($p = .002$). Comorbidity (OCCI score) and age were patient related factors significantly associated to OS, whereas the association between BMI and survival was only borderline significant (Table 3). No association between smoking habits and survival was found in any analyses (data not shown) why this covariate was left out from the final models.

Treatment in Sweden was associated with a 10% decreased mortality rate (HR 0.91 [95% CI 0.80–1.04], $p = .16$) compared to Denmark when adjusting for all covariates (confounders)

Table 3. Cox regression analyses of prognostic factors – multiply imputed data and complete cases.

	Multiply imputed data[a]				Complete cases[a]			
	Univariable analyses[b] ($n = 3188$)		Multivariable analyses[d] ($n = 3118$)		Univariable analyses[b,c]		Multivariable analyses[d] ($n = 2015$)	
Covariate	HR (95% CI)[e]	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Country								
Denmark[g]	1		1		1		1	
Sweden	0.84 (0.74-0.95)	.004	0.90 (0.79-1.01)	.121	0.84 (0.74-0.95)	.004	0.87 (0.72-1.05)	.140
Stage								
I[g]	1		1		1		1	
II	2.11 (1.444–3.08)	<.001	2.28 (1.55–3.36)	<.001	2.02 (1.41–2.89)	<.001	2.23 (1.44–3.46)	<.001
III	5.30 (4.24–6.63)	<.001	4.21 (3.20–5.54)	<.001	5.22 (4.14–6.59)	<.001	4.19 (3.03–5.80)	<.001
IV	8.37 (6.56–10.66)	<.001	5.84 (4.36–7.82)	<.001	8.20 (6.36–10.56)	<.001	5.57 (3.92–7.92)	<.001
Residual tumor*								
No macroscopic residual[g]	1		1		1		1	
Macroscopic residual tumor	3.55 (3.14–4.01)	<.001	2.21 (1.93–2.53)	<.001	3.57 (3.16–4.04)	<.001	2.08 (1.77–2.45)	<.001
Primary treatment*								
Primary surgery[g]	1		1		1		1	
NACT	2.25 (1.99–2.55)	<.001	1.25 (1.08–1.43)	.002	2.25 (1.99–2.54)	<.001	1.34 (1.14–1.59)	<.001
OCCI[f] score	1.37 (1.07–1.75)	.013	1.36 (1.05–1.77)	.020	1.37 (1.07–1.75)	.013	1.43 (1.03–1.98)	.030
Age (per 10 years)*	1.43 (1.36–1.51)	<.001	1.35 (1.27–1.43)	<.001	1.43 (1.36–1.51)	<.001	1.36 (1.27–1.46)	<.001
Histology*								
Serous adenocarcinoma[g]	1		1		1		1	
Mucinous adenocarcinoma	0.41 (0.29–0.58)	<.001	1.42 (0.96–2.11)	.082	0.42 (0.29–0.60)	<.001	1.44 (0.93–2.23)	.105
Endometrioid adenocarcinoma	0.25 (0.17–0.38)	<.001	0.75 (0.49–1.15)	.181	0.25 (0.17–0.37)	<.001	0.68 (0.43–1.07)	.096
Clear cell adenocarcinoma	0.77 (0.55–1.06)	.112	2.16 (1.54–3.01)	<.001	0.72 (0.52–0.99)	.044	2.45 (1.67–3.58)	<.001
Sarcoma	1.89 (1.38–2.59)	<.001	2.68 (1.96 –3.64)	<.001	1.82 (1.35–2.44)	<.001	2.33 (1.68–3.26)	<.001
Rare types	0.70 (0.50–0.99)	.042	1.66 (1.15 –2.39)	.007	0.71 (0.51–0.98)	.038	1.64 (1.10–2.46)	.016
Nutritional status								
Underweight: BMI <18.5	0.99 (0.73–1.34)	.942	1.06 (0.78–1.45)	.705	0.97 (0.72–1.32)	.861	0.90 (0.62–1.32)	.585
Normal weight: 18.5 ≥ BMI <25[g]	1	–	1	–	1	–	1	–
Overweight: 25 ≥ BMI <30	0.83 (0.72–0.96)	.014	0.87 (0.75–1.01)	.076	0.84 (0.72–0.97)	.017	0.83 (0.70–0.98)	.035
Obesity: 30 ≥ BMI <35	0.81 (0.65–1.00)	.054	0.80 (0.64–1.00)	.050	0.80 (0.65–1.00)	.053	0.75 (0.58–0.98)	.032
Severe obesity (BMI ≥35)	0.96 (0.73–1.27)	.772	1.21 (0.92–1.569)	.181	0.94 (0.70–1.26)	.673	1.31 (0.95–1.80)	.101

[a]Univariable and multivariable Cox regression models fitted to multiply imputed data (column 1, $n = 3118$) and complete cases (column 2). In these models, the effects of all variables were assumed to be time-independent. For those variables for which the proportional hazards assumption is not fulfilled (marked with a *) the effects should be interpreted as average effects over time.
[b]Adjusted for age only.
[c]Univariable analyzes based on number of cases with registered values on confounder as described in Table 1.
[d]Adjusted for country, stage, residual tumor, primary treatment, OCCI score, age, histology and BMI.
[e]Hazard Ratio (HR) and Confidence Interval (CI).
[f]Ovarian Cancer Comorbidity Index (OCCI).
[g]Reference group.

Table 4. Multivariable Cox regression analyzes exploring the association between country (Sweden vs. Denmark) and overall survival while adjusting for different groups of confounders, multiply imputed dat[a].

Covariate (s) adjusted for	Hazard ratio (Sweden vs. Denmark)[b]	95% CI[c]	*p* value
Model 1: No adjustment	0.84	0.75–0.95	.004
Model 2: Age	0.84	0.74–0.95	.004
Model 3: Age + OCCI score	0.83	0.74–0.94	.003
Model 4: Age + OCCI score + BMI	0.84	0.74–0.95	.005
Model 5: Stage	0.85	0.75–0.96	.010
Model 6: Stage + histology	0.87	0.77–0.99	.029
Model 7: Primary treatment	0.95	0.84–1.08	.451
Model 8: Primary treatment + Residual tumor	0.89	0.79–1.01	.078
Model 9: All patient, tumor and treatment related factors[d]	0.91	0.80–1.04	.160

[a]These analyses were conducted on the multiply imputed dataset, $n = 3118$. In these models, the log hazard ratios for age, histology, residual tumor and treatment were modeled as a function of time using spline functions due to the proportional hazards assumption not being fulfilled.
[b]Histology, primary treatment, residual tumor and age had time-varying effects whereas country, stage, BMI and OCCI score were time-independent.
[c]Confidence Interval (CI).
[d]Adjustment for age, OCCI score, BMI, stage, histology, primary treatment and residual tumor.

(Model 9, Table 4). To explore which patient, tumor and treatment related factors that would mainly explain the observed difference in survival between Denmark and Sweden, we conducted supplementary Cox analyses including different groups of covariates (Table 4). We observed that including comorbidity in addition to age did not change the HR of country notably, why comorbidity is not thought to explain the observed difference (Model 3 vs. Model 2, Table 4). In contrast, treatment (primary surgery vs. NACT) appeared to explain a substantial part of survival differences, as HR of country changed when including this variable (Model 7 vs. Model 1, Table 4). In fact, including treatment as the only covariate resulted in that country no longer was significantly associated to prognosis (HR 0.95, $p = .45$). This suggests that treatment to a very large extent explains the difference in survival between Denmark and Sweden. A similar, although less pronounced pattern was observed for the stage and histology variables (Model 5 and Model 6 vs. Model 1, Table 4).

As described above, when including all confounding factors the HR = 0.91 of country was not significant ($p = .16$). This implies that the observed survival difference may be explained by known confounders.

Results of analyses based on complete cases were similar to results based on the multiply imputed data (Tables 3 and 5).

Discussion

Summary of principal findings

This study shows that Swedish patients have a more favorable prognosis than Danish and this difference in survival is explained by differences in confounding factors such as stage at diagnosis and especially choice of primary treatment, that is, more upfront primary surgery in Sweden. Comorbidity measured as OCCI score did not explain the observed differences in survival between the two countries.

The prevalence of common comorbidities such as diabetes and hypertension were similar in the cohorts. Arteriosclerotic cardiac disease and chronic pulmonary disease were in our study found to be more common among Swedish patients but, as discussed below, this may, at least partly, be due to registration differences.

Comorbidity could not be confirmed as an explanation for survival differences between Danish and Swedish patients. Comorbidity was a significant prognostic factor in adjusted survival analyses ($p = .02$) but the association between survival and country of origin remained stable when including comorbidity in the analysis. This suggests that comorbidity does not explain the association between survival and country of treatment.

Due to conflicting results regarding the prognostic impact of comorbidity in ovarian cancer, a meta-analysis was carried out by Jiao et al in 2015 [26]. They included eight prospective studies in their analysis comprising a total of 12,681 ovarian cancer patients. They found that the presence of comorbidity was significantly associated with poorer OS (HR 1.20 [95% CI 1.11–1.30]). The association remained robust in sensitivity analyzes. Based on their study and our own results it seems reasonable to state that comorbidity is a prognostic factor in ovarian cancer although other factors such as stage at diagnosis and especially the ability to achieve complete macro radical tumor debulking are more important prognostic factors [27,28].

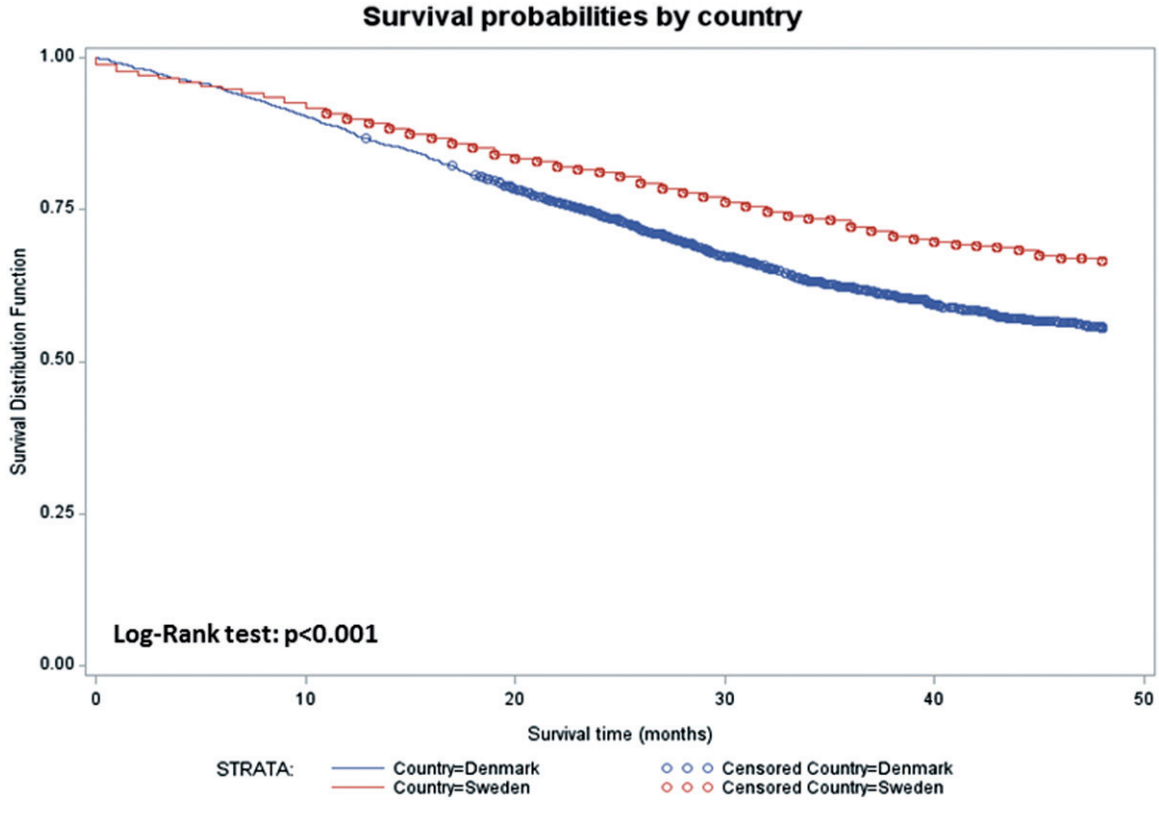

Figure 2. Kaplan–Meier survival plots for estimated overall survival by country of origin.

Strengths and limitations of the study

A major strength of this study is the use of two large comparable clinical databases from two similar Scandinavian countries. Both databases have high coverage from the same period in both countries (2012–2015) and subcohorts of comparable size (1646 and 1472 patients, respectively).

However, some limitations do apply to this register-based design. Comorbidity was the confounding covariate of primary interest in this study and both the DGCD and GynOp contain variables on comorbidity. Unfortunately, some comorbidities are registered rather imprecisely in the clinical databases why we have been forced to make some modifications to the original OCCI. For example, the variable 'Chronic pulmonary disease' is in our study based on a combination of several rather imprecise comorbidity registrations such as 'Chronic cough', 'Wheezing' and 'Other pulmonary disease' (please refer to the notes of Table 2). The fact that comorbidity variables were not the exact same in the two databases may have introduced some imprecision in the calculation of the comorbidity score.

Another concern that may arise from the use of comorbidity information from the DGCD and GynOp is the fact that this information primarily is based on patients self-reports. The validity of information may therefore be questioned. However, previous studies have shown patients' self-reports of comorbidity to be reliable when it concerns comorbidities affecting daily life and/or requiring regular treatments/appointments [29–31]. Further, the prevalence of the four specific comorbidities included in the calculation of the comorbidity score in our study is in accordance with prevalence previously reported among ovarian cancer patients [32–34]. Based on this, we believe that the comorbidity information collected from the DGCD/GynOp and classified with the OCCI has provided a useful, although not perfect, estimate of clinically important comorbidity affecting daily life of ovarian cancer patients in both countries.

GynOp includes only surgically treated patients as opposed to DGCD that contains information on all ovarian cancer patients regardless of treatment. This selection of Swedish patients may bias results as surgically treated patients may be 'healthier' (i.e., younger, less advanced stage) than patients not offered surgery. To minimize possible selection bias we have excluded 295 Danish patients who did not receive any surgical treatment.

We decided to use MI to handle missing data to minimize potential bias. MI was performed under the assumption of a MAR mechanism, namely that missingness of a confounder does not depend on the actual level of the confounder given information in remaining confounders as well as survival time. Possible misspecification of the imputation and analysis models as well as MAR not being fulfilled are all potential sources to bias.

Possible explanations for international differences in ovarian cancer survival

Major international differences in ovarian cancer survival exist and the reasons for this are not yet clear [35,36]. Among proposed causes are differences in prevalence of histological subtypes (i.e., different aggressiveness of tumor cells), different stage distribution at time of diagnosis and different access to proper cancer treatment. These explanations may very well explain survival differences across continents but it is harder to explain substantial differences in survival between two very similar Scandinavian countries and populations. Comorbidity (i.e., patients' general health) was thought to be a contributing explanatory factor, but our study did not confirm this hypothesis. Based on results of the present study, we do however dare to suggest and discuss other possible mechanisms behind the observed survival differences in Swedish and Danish ovarian cancer patients.

Previous publications have identified a less favorable stage distribution among Danish ovarian cancer patients compared to other countries and suggested that diagnostic delay contributes to poorer Danish survival [37]. In our material, a substantial difference in stage IV distribution was observed as more Danish patients were diagnosed in stage IV (17.2% vs. 10.7%). In contrast, more Swedish than Danish patients were diagnosed in stage III (55.9% vs.44.6%) and the frequencies of stage I-II were comparable. Further, it is worth to note that more Danish than Swedish patients were underweight (BMI <18.5) which may reflect more advanced disease

Table 5. Multivariable Cox regression analyzes exploring the association between country (Sweden vs. Denmark) and overall survival while adjusting for different groups of confounders, complete cases[a].

Covariate (s) adjusted for	Hazard ratio (Sweden vs. Denmark)[b]	95% CI[c]	*p* value
Model 1: No adjustment ($n = 3118$)	0.84	0.75–0.95	.004
Model 2: Age ($n = 3118$)	0.84	0.75-0.95	.005
Model 3: Age + OCCI score ($n = 3118$)	0.83	0.74–0.94	.003
Model 4: Age + OCCI score + BMI ($n = 2651$)	0.81	0.71–0.93	.002
Model 5: Stage ($n = 2669$)	0.86	0.75–0.99	.033
Model 6: Stage + histology($n = 2326$)	0.84	0.71–0.99	.038
Model 7: Primary treatment ($n = 3106$)	0.96	0.85–1.08	.515
Model 8: Primary treatment + residual tumor ($n = 2923$)	0.92	0.81–1.04	.196
Model 9: All patient, tumor and treatment related factors[d] ($n = 2015$)	0.87	0.72–1.05	.148

[a]Complete case analyses based on number of cases with information on all variables included in the analyzes (n given in parenthesis). In these models, the log hazard ratios for age, histology, residual tumor and treatment were modeled as a function of time using spline functions due to the proportional hazards assumption not being fulfilled.
[b]Histology, primary treatment, residual tumor and age had time-varying effects whereas country, stage, BMI and OCCI score were time-independent.
[c]Confidence Interval (CI).
[d]Adjustment for age, OCCI score, BMI, stage, histology, primary treatment and residual tumor.

(i.e., cancer wasting) among Danes. However, before drawing a conclusion regarding a 'true' difference in the occurrence of the most advanced stage in Denmark and Sweden, some potential confounders must be considered.

Firstly, more Danish than Swedish patients were classified as having 'No macroscopic residual' (69.4% vs. 64.6%) and correspondingly, the frequency of 'Macroscopic residual' was higher among Swedish patients (30.6 vs. 35.4%). This finding speaks against a major difference in stage IV distribution.

Secondly, the standard method for preoperative evaluation is different in Denmark and Sweden. Whereas PET/CT is routinely used for diagnostic work up in patients referred with a Risk of Malignancy index above 200 in Denmark, the standard image modality for diagnosis of a pelvic mass in Sweden is CT of thorax/abdomen/pelvis. As PET/CT in previously published studies has been found to cause stage migration (mainly from stage III to stage IV), this difference in image modality preference may contribute to the observed difference in stage distribution in our two sub-cohorts [38,39].

Another possible explanation for the observation of differences in stage III/IV distribution may be that the data quality in the Swedish cohort is not as solid as the Danish data and also that the fraction of missing data in the Swedish cohort was larger. However, based on results of our exploratory analyses of missing data, we do not believe in this explanation. These analyses revealed that Swedish patients with missing information had a better prognosis compared to complete cases. They do therefore not exclusively represent cases of advanced disease but rather poor compliance in regard to data registration among Swedish gynecologists.

Our results support that differences in stage distribution between Danish and Swedish patients exists, and our results of multivariable models suggest that some of the favorable prognosis related to Swedish ovarian cancer patients may be explained by the stage variable.

Differences in patient selection for NACT may be another direction to look in search of explanations for survival differences between Denmark and Sweden. We found a much higher frequency of NACT use in Denmark compared to Sweden (29.7% vs. 17.0%, $p < .001$) and NACT was associated to poorer survival compared to primary debulking surgery. Furthermore, our explorative survival analyses revealed that the treatment variable explained a substantial part of the positive prognostic effect of Sweden.

It is interesting that choice of primary treatment apparently differs so much between Denmark and Sweden, and even within the two countries the use of NACT has previously been shown to vary greatly between centers [18,40]. Possible differences in treatment strategies and policies at the different tertiary centers should be further analyzed and discussed in order to provide optimal and more equal preoperative assessment and treatment to patients throughout the two countries.

Recommendations regarding standard oncological treatment are similar in Denmark and Sweden: Six series of carboplatin (AUC5-6) combined with paclitaxel (175mg/m^2) are given after primary debulking surgery and three series are given before interval debulking surgery. Bevacizumab may be added if complete macroscopic tumor debulking cannot be achieved surgically. Unfortunately, data on oncological treatment were not available for this study, why analyzes on whether Swedish medical subspecialist gynecologic oncologists order more aggressive second and third line chemotherapy treatment, initiate treatment earlier or have a tradition of ordering more lines of treatment than the Danish medical oncologists, were not possible. Also, we did not have valid information on recurrences and could therefore not investigate the association between country and progression-free survival. However, as different treatment strategies in regard to adjuvant chemotherapy may affect overall as well as progression free survival this should be investigated in future studies.

Conclusions

We found that Swedish surgically treated ovarian cancer patients have a better prognosis than Danish patients. The prevalence of most comorbidities was similar in these two Scandinavian countries and we found no evidence supporting the hypothesis that comorbidity is the explanation for excess mortality among Danish patients. In contrast, other tumor and treatment related variables, especially differences in primary treatment strategies, seemed to contribute to the more favorable prognosis among Swedish patients. Future research should aim on identifying differences in choice of primary treatment as well as adjuvant therapy. This may lead to valuable exchange of experiences and ensure implementation of 'best practice'.

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Disclosure statement

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