

Improved survival of patients with ovarian cancer in Northern Denmark, 1985-2004

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Summary

Objective: Ovarian cancer is a serious disease with a high mortality. Our aim was to examine changes in the survival of patients with ovarian cancer in Northern Denmark.

Study design and setting: Patients (no. = 3,719) with an incident discharge diagnosis of ovarian cancer (1985-2004) from any hospital in four Danish counties (population, 1.6 million) were included and tracked for mortality through the Danish Civil Registration System. We determined survival and mortality rates stratified by age, and used Cox proportional hazard regression analyses to assess changes over time.

Results: Overall survival rate improved between 1985 and 2004. One-year survival increased from 61% to 73%, and five-year survival from 30% to 38%. Compared with the period 1985-1989 the age-adjusted one-year mortality rate ratio (MRR) was 0.65 (2000-2004) and the age-adjusted five-year MRR was 0.80 (1995-1999). The improvement was most pronounced in patients older than 40 years.

Conclusion: The survival of ovarian cancer patients has improved in Denmark in recent decades. This change may be the result of improved treatment.

Key words: Ovarian neoplasm; Outcome research; Survival.

Introduction

Ovarian cancer is a serious disease with a high mortality. With about 600 new cases per year, ovarian cancer is the fifth most common cancer among Danish women (incidence rate, 14 per 100,000 persons/year in 1999) [1]. For unknown reasons, Danish ovarian cancer patients have a lower survival rate than ovarian cancer patients from other countries (5-year relative survival in Denmark: 30.5%, Sweden: 44.2% Finland: 36.9%) [2-4].

The treatment of ovarian cancer in most cases consists of primary surgical treatment and postoperative chemotherapy [5-7]. In Denmark treatment patterns have generally been primary surgery at local hospitals followed by centralised oncological treatment. Adjuvant radiotherapy for ovarian cancer has not been used in Denmark since 1988. Surgical treatment changed little during the period 1985 to 2004, and has been offered in general obstetrical and gynaecological departments, in oncology-gynaecology centres, and in departments of general surgery. Until 1994 Danish postoperative chemotherapy consisted of combinations of cisplatin with

or without other cytostatics. Subsequently, chemotherapy with paclitaxel has been standard, following the findings of randomised clinical trials that showed improved survival with cisplatin-paclitaxel compared to cyclophosphamide-cisplatin [8, 9].

The impact of these changes in ovarian cancer treatment has not been assessed. Since the prognosis of ovarian cancer patients is poor, it is important to monitor survival as an indicator of treatment efficacy. We therefore aimed to examine changes in mortality and survival in ovarian cancer patients between 1985 and 2004 by using updated data from the population-based regional hospital discharge registries in Northern Denmark.

Materials and Methods

We conducted the study in four Danish counties (North Jutland, Aarhus, Ringkjøbing and Viborg) with approximately 1.6 million inhabitants. Patients with an incident discharge diagnosis of ovarian cancer between 1 January 1985 and 31 March 2004 were included and followed until death, emigration, or 31 January 2005.

Identification of the patients

Hospital discharge registries

We identified patients with ovarian cancer by searching the discharge diagnoses codes stored within the Aarhus University Hospital Research Database. The database carries key information on all patients from the hospital discharge registries in the

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four counties. Since 1977, all Danish counties have established hospital discharges registries that are used routinely to monitor hospital admissions and discharges, waiting lists, operations, and treatment (in Viborg County since 1972). Data includes civil registration number (CPR), dates of admission and discharge, the surgical procedure(s) performed, and up to 20 discharge diagnoses (given by the physicians), which are classified according to the Danish version of the International Classification of Diseases (ICD) (8th revision until the end of 1993 and 10th revision thereafter [10]). The ICD-8 codes used were 183.00-03, 183.08-09, and the ICD-10 codes used were C56.x.).

Study period

Our study included all patients who were registered for the first time in the Aarhus University Hospital Research Database with one of the 20 ovarian cancer discharge diagnoses (data from Ringkjøbing County has only been included since 1995). To avoid including prevalent cases, patients registered with ovarian cancer discharge diagnoses in the period 1977 to 1984 (for Ringkjøbing County in the period 1977-1994) were excluded.

The Danish Civil Registration System

Since 1968, a unique 10-digit civil registration number has been assigned to each Danish citizen by the Central Office of Civil Registration, and this number was used to link data from the registries. The Civil Registration System also contains information on vital status, date of death, and the residence of all Danish citizens. We required that the patients reside in one of the study counties at the time of diagnosis.

Statistical analysis

Survival

The study cohort was linked by the civil registration number to the Civil Registration System to obtain information on vital status. All cases were followed from the date of the ovarian cancer diagnosis until death, emigration, or January 31, 2005.

To visualise survival in the five-year calendar periods, Kaplan-Meier survival curves were constructed for the periods 1985-1989, 1990-1994, 1995-1999 and 2000-2004. The one- and five-year survival rates were estimated within three age strata: < 40 years, 40-59 years, \geq 60 years.

Mortality

Cox proportional hazards regression analyses were used to compute the mortality rate ratios for the five-year calendar periods, assigning 1985-1989 as the reference period. The age-adjusted one- and five-year mortality rate ratios were estimated with the same reference period. Estimates are presented with 95% confidence interval (95% CI). Statistical analyses were performed with the use of SAS[®] software (version 9.13, SAS Institute, Cary, N.C.).

Results

A total of 3,719 patients were diagnosed with ovarian cancer for the first time during the 19-year period between 1985 and 2004.

Age characteristics of ovarian cancer patients

The median age was consistently about 63 years over all time periods. Between 7% and 8% of the ovarian cancer patients were younger than 40 years; 32%-39%

were 40-59 years of age, and between 54% and 61% were older than 60 years (Table 1). Thus there was little change in the age distribution of ovarian cancer patients over the study period.

Table 1 — Number of women with a first-time diagnosis of ovarian cancer in three age groups (1985-2004).

	1985-1989	1990-1994	1995-1999*	2000-2004**
< 40 years	62 (7%)	62 (7%)	87 (8%)	66 (7%)
40-59 years	281 (34%)	287 (32%)	394 (36%)	344 (39%)
\geq 60 years	490 (59%)	542 (61%)	624 (56%)	480 (54%)
Total	833	891	1105	890

*Since 1995 data from the fourth county (Ringkjøbing County) have been included.

**This period is nine months shorter than the other three five-year periods.

Survival

The overall survival curves for the four periods showed improved survival over the years (Figure 1). Compared to patients diagnosed during 1985-1989, those registered during 2000-2004 had about 10% lower mortality rates. The survival advantage was present as early as six months after the qualifying hospital discharge.

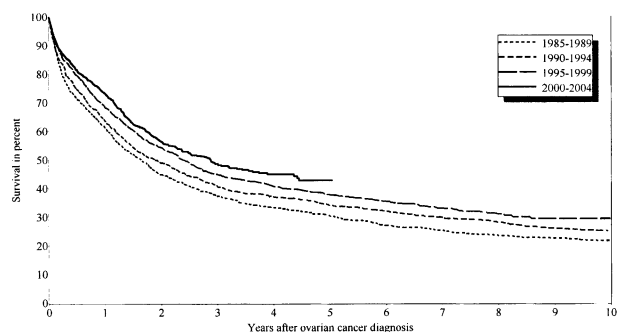


Figure 1. — Survival of ovarian cancer patients in four time periods.

The overall one-year survival improved from 61% to 73% during the period 1985 to 2004, and the overall five-year survival likewise improved from 30% in the period 1985-1989 to 38% in the period 1995-1999 (Table 2).

Age-adjusted survival

One-year survival improved from the period 1985-1989 to the period 2000-2004. For the youngest women there was a moderate increase from 92% to 94%. For women 40-59 years and for women 60 years or older, the one-year survival increased from 75% to 84% and from 50% to 62%, respectively (Table 3).

The five-year survival also improved between 1985-1989 and 1995-1999. The increase was most pronounced for women 40-59 years, among whom an increase in survival from 37% to 53% was observed. Among those aged 60 years or older the improvement was more moderate, rising from 21% to 24% (Table 3).

Table 2 — One- and five-year survival and one- and five-year mortality rate with the period 1985-1989 as a reference. Estimates are presented with 95% confidence intervals (95% CI).

	1985-1989	1990-1994	1995-1999	2000-2004
Number of patients	833	891	1105	890
Mean age (years)	63	64	63	62
<i>One year</i>				
Survival in percent	61%	64%	68%	73%
	(58%-65%)	(60%-67%)	(66%-71%)	(70%-76%)
Crude mortality rate ratio	1	0.91	0.76	0.63
	(reference)	(0.78-1.07)	(0.65-0.89)	(0.53-0.75)
Age-adjusted mortality rate ratio	1	0.89	0.77	0.65
	(reference)	(0.76-1.04)	(0.66-0.90)	(0.55-0.77)
<i>Five years</i>				
Survival in percent	30%	34%	38%	—
	(27%-34%)	(31%-37%)	(35%-41%)	
Crude mortality rate ratio	1	0.90	0.79	—
	(reference)	(0.80-1.01)	(0.71-0.88)	
Age-adjusted mortality rate ratio	1	0.88	0.80	—
	(reference)	(0.78-0.99)	(0.72-0.90)	

Table 3 — One- and five-year absolute survival for ovarian cancer patients in three different age groups. Estimates are presented with 95% confidence intervals (95% CI) in parenthesis.

	1985-1989	1990-1994	1995-1999	2000-2004
<i>< 40 years</i>				
Number of patients	62	62	87	66
1-year survival	92%	90%	88%	94%
	(82%-97%)	(80%-95%)	(80%-94%)	(85%-98%)
5-year survival	73%	80%	74%	—
	(60%-82%)	(68%-88%)	(64%-82%)	
<i>40-59 years</i>				
Number of patients	281	287	394	344
1-year survival	75%	78%	85%	84%
	(70%-80%)	(73%-82%)	(81%-88%)	(80%-88%)
5-year survival	37%	46%	53%	—
	(31%-43%)	(40%-52%)	(47%-57%)	
<i>≥ 60 years</i>				
Number of patients	490	542	624	480
1-year survival	50%	53%	55%	62%
	(45%-54%)	(49%-57%)	(51%-59%)	(58%-67%)
5-year survival	21%	22%	24%	—
	(18%-25%)	(19%-26%)	(20%-27%)	

Mortality

Overall, the one-year mortality rate decreased 37% between 1985-1989 and 2000-2004; the five-year mortality rate decreased 21% between 1985-1989 and 1995-1999 (Table 2). There were similar decreases in the age-adjusted mortality rates (Table 2).

Discussion

We found that the overall survival of Danish ovarian cancer patients improved between the years 1985 and 2004. The difference in survival across the age groups was most pronounced during 1985-1989; thereafter the differences decreased. The most marked improvement in survival was found among ovarian cancer patients aged 40-59 years and to a lesser degree among the oldest of the ovarian cancer patients.

A previous study based on data from the Danish Cancer Registry (including 19,476 patients) found improved

five-year survival over the period 1943 to 1987 (22.3% vs 30.4%) [11]. The later survival statistics correlate well with our findings for the period 1985-1989, in which we observed a five-year survival of 30%. In contrast to our study and that by Kjær and Storm, a third Danish analysis found no improvement in survival between 1973-1978 and 1981-1986 [12]. This analysis was based on data from the Hospital Discharge Registry and the Danish Cancer Registry and included 412 patients with ovarian cancer, none of whom had borderline tumours.

In several previous European studies, ovarian cancer survival has likewise increased since the mid-1970s [4, 13-15]. However, these countries have consistently reported a higher survival rate than our study. A Norwegian study showed a five-year survival improvement from 39% during 1975-1979 to 43% during 1990-1994 [14]. A study from the Netherlands, including 568 patients (without borderline tumours), showed that patients diagnosed in 1981-1985 had a better five-year survival than patients diagnosed in 1975-1980 (48% vs 28%) [15].

Our study was based on data from a defined cohort that contains all ovarian cancer patients from approximately 30% of the Danish population. The study was large and well-defined. We accomplished complete vital status follow-up by using the Civil Registry System. Data on cancer in Denmark are usually extracted from the nationwide Danish Cancer Registry because the completeness and accuracy of data in this registry are well established [16, 17]. On the other hand, there is often a long delay between the time data submission to the Cancer Registry and the time the data are available for scientific purposes. Therefore, data from the Cancer Registry are not optimal for an ongoing quality assessment of recent improvements in ovarian cancer treatment.

Another disadvantage is that the hospital discharge registries are not without some degree of misclassification concerning ovarian cancer diagnoses. Malignant ovarian tumours include borderline tumours and invasive tumours. The prognosis of patients with borderline ovarian tumours is far better than that for patients with invasive disease. Overall five-year disease-related survival rates are respectively 86% [18] and 32% [19]. Borderline tumours comprised 16% of ovarian cancers during 1981-1991 and 18% during 1994-2003 [20]. It thus seems unlikely that an increase in the proportion of borderline tumours can entirely account for the increased survival observed in our study. The ICD-10 (and ICD-8) classification comprises no specific code for borderline tumours; these tumours therefore cannot be separated from invasive ovarian cancer and are thus a potential source of bias in hospital discharge registries. We validated the ovarian cancer diagnoses by comparing data from the hospital registry to data from the Danish Cancer Registry [20]. We found that ovarian cancer diagnoses had a completeness of 96% in the hospital discharge registry and the PPV (positive predictive value) was 87%. These findings indicate that our study had high validity and that data from hospital discharge registries can be

used to monitor survival. If patients with borderline tumours were included in the data, the survival estimates would be overestimated.

Several factors may influence the outcome of cancer such as biology of the tumour, presence of other diseases (comorbidity), quality of the diagnostic test, treatment, and clinical performance and organisation of the health system [21]. The slightly better prognosis of ovarian cancer over time in our study was most likely partly due to the more extensive surgery in later years and the use of more effective chemotherapy. We have no information about stage of the ovarian cancer in our analysis, but during our study period increasing use of diagnostic ultrasound and use of the blood test CA-125 may have resulted in an earlier diagnosis. Hence, we cannot exclude the possibility that improvements in survival stem from earlier diagnoses. Life expectancy has increased in the general population in the last decades [22], and since we did not adjust for this fact, the improvement in prognosis of ovarian cancer patients may in part be attributable to a reduced mortality for all Danes. On the other hand, Danish women have a slightly lower life expectancy than women in Norway and Sweden. A heavy burden of tobacco smoking in Danish women has been reported as the key explanatory factor behind the lower life expectancy [23], but also a degree of higher comorbidity in Danish women might be an important factor. The low life expectancy compared to other countries can thus be a very important issue in comparing survival estimates.

Conclusion

The survival of ovarian cancer patients has improved in Denmark in recent decades, and this change is most pronounced in women older than 40 years. These results may suggest a benefit of improved treatment.

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