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The influence of comorbidity on mortality in ovarian cancer patients

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HIGHLIGHTS

- The influence of common comorbidity diagnoses on mortality was evaluated in more than 11000 women with ovarian cancer.
- Thromboembolism, hematologic complications and infections had a pronounced effect on mortality rates.
- The impact of comorbidity was most apparent among those with less aggressive tumours and younger age.

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ABSTRACT

Background. Ovarian cancer is a severe disease with a peak incidence in the older age groups where concurrent morbidity is common and could potentially influence mortality rates.

Objectives. The aim was to study the influence of common comorbidity diagnoses on mortality in ovarian cancer patients.

Methods. The study population was patients with ovarian cancer in Sweden 1993–2006 (n = 11.139) identified in the national Cancer Register. Comorbidity data was obtained from the Patient Register and mortality from Cause of Death Register. Mortality was analyzed with Cox' proportional hazards models and subgroup analyses were performed by age and tumor histology.

Results. Almost all of the assessed comorbidities increased mortality in ovarian cancer patients. Thromboembolism was the most hazardous comorbidity (HR = 1.95, <1 year after cancer diagnosis and HR = 7.83, 1–5 years after cancer diagnosis) followed by hematologic complications (HR = 1.84 and 7.11 respectively) and infectious disease (HR = 1.48 and 5.28 respectively). The occurrence of diabetes mellitus and hypertension had less impact on mortality.

Conclusion. Thromboembolism, hematologic complications and infections had a pronounced effect on mortality rates in women with ovarian cancer. The impact of comorbidity was mainly apparent among those with a more prosperous prognosis, such as longer time since cancer diagnosis, less aggressive tumors and younger age.

Introduction

Ovarian cancer has the highest mortality rate among all gynecological malignancies with around 40% surviving five years [12,23]. The incidence, which is 10.4 per 100,000 person years, is increasing by age and is approximately five times higher for women over 65 years of age [7]. The relation to higher age makes the presence of other diseases an important factor affecting cancer morbidity [22] and mortality. Both chronic comorbidities and acute conditions influence the treatment and prognosis of ovarian cancer [5,6,8]. In addition age and comorbidity influence the choice of treatment and prognosis [14–17].

The aim of this study was to estimate the effect of comorbidity on mortality in patients with ovarian cancer in relation to time of cancer diagnosis. We used information from Swedish health registers and assessed the influence of age at diagnosis and histologic tumor type.

Methods

The Cancer and Comorbidity Database

The Cancer and Comorbidity Database (CaCom) is a compilation of Swedish national health registries as described previously [22]

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and contains all cases of cancer registered in the Swedish National Cancer Register (NCR) between 1992 and 2006. The database includes approximately 1.5 million control individuals randomly sampled from the Register of the Total Population (RTP) held by Statistics Sweden, and matched to have the same distribution with respect to age, sex and calendar year as all cases of cancer in the database. These individuals (cancer cases and population controls) are linked to the nationwide Swedish Cause of Death Register to obtain date and cause of death for deceased individuals, and with the Swedish Patient Register to obtain in-patient discharge data for all hospitalizations in these individuals occurring from 1987 up to 2006. In this study we used the database to explore predefined comorbidities among patients with ovarian cancer as well as in a matched control group.

Study population

The study population was defined as all patients in the CaCom database diagnosed with ovarian cancer from January 1st 1993 up to November 30th 2006. The patients should be alive at 30 days after diagnosis in order to exclude those "fatal at diagnosis" and restrict the study to ovarian cancer patients potentially amenable to treatment in routine medical care. Patients with a pathology diagnosis (SNOMED, Systematized Nomenclature of Medicine, classification) of borderline tumor or tumors considered as benign (i.e. thecoma, cystadenoma) were excluded from the analyses. Pathological diagnoses were grouped into six categories: *high risk epithelial* including serous and endometroid adenocarcinomas, anaplastic, small cell and poorly differentiated carcinomas; *medium risk epithelial* including mucinous adenocarcinomas, clear cell carcinomas, and mesonefroid cancers; *germ cell tumors*, *stroma cell tumors and sarcomas*, which were classified according to standard definitions. The category *other tumors* included varying histology such as poorly defined tumors, squamous cell cancers and neuroendocrine tumors.

Control group

To each cancer case, five controls matched by year of birth, were randomly selected among the 0.75 million control women in the CaCom database. Each control was assigned the same date for start of follow-up as her matched case; this date was the date of diagnosis for ovarian cancer plus an additional 30 days, and defined as the index date. The controls were not allowed to have an ovarian cancer diagnosed before the corresponding matched case date of diagnosis, and were censored on the relevant date if they contracted an ovarian cancer diagnosis during the follow-up.

Comorbidities

In CaCom we identified comorbidities by diagnostic codes according to the ICD-classification, ninth and tenth revision (ICD-9 and ICD-10). We selected 6 major disease groups; hematologic complications, thromboembolic event, cardiovascular disease (excluding acute cardiac infarction), infectious disease, diabetes mellitus and hypertension [22]. Comorbidity was registered between one year before ovarian cancer diagnosis and five year after diagnosis.

Sources of data

The Swedish Cancer Register was founded in 1958 and contains information about clinical and histological diagnoses and date and place of living at diagnosis. It is updated annually and reported valid information on more than 97% of all patients with cancer [2]. The Cancer Register converts all diagnoses recorded by the current ICD and ICDO version into ICD 7 in order to facilitate comparisons over time.

The Swedish Patient Register includes data on dates of each hospital admission, main discharge diagnosis and secondary diagnoses by ICD codes. The routines of recording and forwarding diagnoses are standardized across Sweden. The Cause of Death Register contains data on dates and causes of death for Swedish residents since 1961. The coverage is more than 99.5%.

Statistical analyses

Relative 5-year mortality rates were calculated using Cox' proportional hazard models and are presented as Hazard Ratios (HRs) with 95% confidence intervals (CIs). The 5-year mortality rates for women with ovarian cancer were calculated according to comorbidities diagnosed within one year after the cancer diagnosis and for comorbidities diagnosed between 1 and 5 years from cancer diagnosis. For the control group the mortality rates were calculated for comorbidities diagnosed within one year after the index date and for comorbidities diagnosed between 1 and 5 years from the index date. P-values for differences in HR between women with ovarian cancer and controls were calculated with a significance level of 0.05. For the women with ovarian cancer, we estimated the 5-year mortality rate by occurrence of comorbidity and stratified by histology group (high risk/medium risk epithelial tumors) and by age at ovarian cancer diagnosis (≤59 years/>60 years). In all adjusted analyses we included age at cancer diagnosis as a continuous variable in the models.

The study was approved by one of the regional ethical boards at Karolinska Institutet, Stockholm.

Table 1
Numbers and survival rate of women with ovarian cancer by age at diagnosis, time period, histology and comorbidity.

			1-Year survival		5-Year survival	
	N	(%)	N	(%)	N	(%)
All	11,139		9193	(82.5)	5201	(46.7)
Age at cancer diagnosis (years)						
–49	1867	(16.8)	1739	(93.1)	1270	(68.0)
50–69	5443	(48.9)	4782	(87.9)	2731	(50.2)
70–	3829	(34.4)	2672	(69.8)	1200	(31.3)
Year of ovarian cancer diagnosis[a]						
1993–1996	3438	(30.9)	2728	(79.3)	1437	(41.8)
1997–2001	3715	(33.4)	3120	(84.0)	2024	(43.7)
Histologic type						
Epithelial, high risk[b]	8567	(76.9)	7078	(82.6)	3638	(42.5)
Epithelial, medium risk[c]	1504	(13.5)	1220	(81.1)	876	(58.2)
Germ cell tumor	146	(1.3)	140	(95.9)	130	(89.0)
Stroma cell tumor	452	(4.1)	437	(96.7)	390	(86.3)
Sarcomas	202	(1.8)	115	(56.9)	43	(21.3)
Other	268	(2.4)	203	(75.7)	124	(46.3)
Comorbidity						
Hematologic complications	1460	(13.1)	–	–	381	(26.1)
Thromboembolic events	929	(8.3)	–	–	209	(22.5)
Cardiovascular disease	1324	(11.9)	–	–	424	(32.0)
Infectious disease	1277	(11.5)	–	–	390	(30.5)
Diabetes mellitus	565	(5.1)	–	–	190	(33.6)
Hypertension	1244	(11.2)	–	–	525	(42.2)

[a] Women with ovarian cancer diagnosis after 2001 were excluded due to incomplete survival data.
[b] High risk epithelial tumors included serous and endometroid adenocarcinomas, anaplastic, small cell and poorly differentiated carcinomas.
[c] Medium risk epithelial tumors included mucinous adenocarcinomas, clear cell carcinomas, and mesonefroid cancers.