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Evaluation of prevalent and incident ovarian cancer co-morbidity

K Stålberg*[,1], T Svensson[2], F Granath[2], H Kieler[2], B Tholander[3] and S Lönn[4,5]

[1]Department of Women's and Children's Health, Uppsala University, 75185 Uppsala, Sweden; [2]Department of Medicine, Centre for Pharmacoepidemiology, Karolinska Institutet, 17177 Stockholm, Sweden; [3]Department of Oncology, Radiology and Clinical Immunology, University Hospital, 75185 Uppsala, Sweden; [4]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, 17177 Stockholm, Sweden; [5]Research and Development, AstraZeneca, 15185 Södertälje, Sweden

BACKGROUND: The peak in incidence of ovarian cancer occurs around 65 years and concurrent increasing risk by age for a number of diseases strongly influence treatment and prognosis. The aim was to explore prevalence and incidence of co-morbidity in ovarian cancer patients compared with the general population.

METHODS: The study population was patients with ovarian cancer in Sweden 1993–2006 ($n = 11\,139$) and five controls per case ($n = 55\,687$). Co-morbidity from 1987 to 2006 was obtained from the Swedish Patient Register. Prevalent data were analysed with logistic regression and incident data with Cox proportional hazards models.

RESULTS: Women developing ovarian cancer did not have higher overall morbidity than other women earlier than 3 months preceding cancer diagnosis. However, at time of diagnosis 11 of 13 prevalent diagnosis groups were more common among ovarian cancer patients compared with controls. The incidence of many common diagnoses was increased several years following the ovarian cancer and the most common diagnoses during the follow-up period were thromboembolism, haematologic and gastrointestinal complications.

CONCLUSION: Women developing ovarian cancer do not have higher overall morbidity the years preceding cancer diagnosis. The incidence of many common diagnoses was increased several years following the ovarian cancer. It is crucial to consider time between co-morbidity and cancer diagnosis to understand and interpret associations.

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Ovarian cancer has the highest mortality rate among all gynaecological malignancies with an overall 5-year survival proportion in the Nordic countries of around 40% (Klint *et al*, 2010; Storm *et al*, 2010). The incidence in the Nordic countries is 10.4 per 100 000 person years (2004–2008) but is approximately five times higher for women over 65 years of age (Engholm *et al*, 2010). The steep increase in incidence by age makes the presence of other diseases an important factor affecting cancer morbidity and mortality. Both chronic co-morbidities and acute conditions influence the treatment and prognosis of ovarian cancer (Cloven *et al*, 1999; Elit *et al*, 2008; Fader *et al*, 2008).

It is a challenge to evaluate the influence of co-morbidity and the knowledge of the significance in ovarian cancer patients is limited. In studies with the aim to evaluate the impact of patient's total co-morbidity as a predictor of outcome, an index can be valuable (de Groot *et al*, 2003). However, if a specific co-diagnosis is to be studied, very large study populations are needed to achieve sufficient power, as ovarian cancer is a rare diagnosis. Another issue is that some diagnoses are characterised as acute conditions and is preferably measured as incidence, while others are more chronic in their character, and are best described in prevalence analyses. Co-morbidity can be a consequence of cancer, cause cancer, or by chance, be diagnosed at the same time as the cancer. Accordingly, the time window in relation to cancer diagnosis must be taken into consideration.

The aim of this study was to estimate prevalent and incident pre-defined co-morbidity at certain time periods in relation to ovarian cancer diagnosis and to evaluate the occurrence in comparison with the general population, using the Swedish national-based databases.

MATERIALS AND METHODS

The Cancer and Co-morbidity Database

The Cancer and Co-morbidity Database (CaCom) is a compilation of Swedish national health registries and contains all cases of cancer registered in the Swedish National Cancer Register (NCR) between 1992 and 2006; and in addition, there is information on any prior cancers reported in these same individuals in the period from 1958 to 1991. The database also includes ~1.5 million control individuals randomly sampled from the Register of the Total Population (RTP) 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 all in-patient discharge data for all hospitalisations in these individuals occurring from 1987 up to 2006. In this study, we used

*Correspondence: Dr K Stålberg, E-mail: karin.stalberg@kbh.uu.se
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the database to explore pre-defined co-morbidities among patients with ovarian cancer.

Patient population

The study patient population was defined as all patients in the CaCom database diagnosed with ovarian cancer (ICD-7 code 175) from 1 January 1993 up to 30 November 2006. The patients should be alive at 30 days after diagnosis 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 classification) of borderline tumour or tumours considered as benign (i.e., thecoma and cystadenoma) were excluded from the analyses. Pathological diagnoses were grouped into six categories; *high-risk epithelial* including the serous and endometroid adenocarcinomas, anaplastic, small cell and poorly differentiated carcinomas; *medium-risk epithelial* including the mucinous adenocarcinomas, clear cell carcinomas, and mesonefroid cancers; *germ cell tumours, stroma cell tumours* and *sarcomas* are classified according to standard definitions. The category *other tumours* includes varying histology such as poorly defined tumours, squamous cell cancers and neuroendocrine tumours.

Control population

To each cancer case, up to five controls matched by year of birth, were randomly selected among the 0.75 million control women in the CaCom database. The controls were assigned the same date for start of follow-up as the matched case; this date was defined as diagnosis date for ovarian cancer plus 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.

Sources of data

The Swedish Cancer Register was founded in 1958 and contains information about clinical and histological diagnosis and date and place of living at diagnosis. It is updated annually and reported valid information on >97% of all patients with cancer (Barlow *et al*, 2009). The Cancer Register converts all diagnoses into ICD-7 in order to be able to make comparisons over time.

The Swedish Patient Register includes data on dates of each hospital admission, main discharge diagnosis and secondary diagnoses if occurring. The routines of recording and forwarding diagnoses are standardised across Sweden. In CaCom, we identified 40 different co-morbidities from the Swedish Patient Register by diagnostic codes according to the ICD classification, ninth and tenth revision (ICD-9 and ICD-10), which were categorised into 13 major disease groups (see Appendix Table A1).

The Cause of Death Register contains data on dates and causes of death for Swedish citizens since 1961. The coverage is >99.5% and data are updated annually.

Statistical analyses

The prevalence of a specified co-morbidity was defined as having one of the selected diseases either as a primary or as a secondary discharge diagnosis from 10 years before the ovarian cancer diagnosis up to 30 days after. The estimates on relative prevalence were calculated with a conditional logistic regression model, conditioned on age in 5-year strata and calendar year of diagnosis. Results were presented as odds ratios (ORs) with 95% confidence intervals (CIs). Additionally, analyses of the prevalence of co-morbidity for the most common histological tumour types, high-risk and medium-risk epithelial tumours were performed.

The incidence of specified condition was defined as having an admission in the period starting at 30 days after the ovarian cancer diagnosis until end of follow-up. End of follow-up was the first date of an admission with the diagnosis of interest, date of death, date of ovarian cancer diagnosis for a control subject, or 31 December 2006, whichever came first.

The analysis of incidence can be considered as a series of exposed and unexposed individuals with different outcomes of interest, where the exposure is an ovarian cancer diagnosis. Accordingly, we used Cox proportional hazards models for these analyses and the results are presented as hazard ratios (HR) together with 95% CIs. The proportional hazards assumption was investigated by allowing different HRs during the first year of follow-up and the subsequent years.

Sensitivity analyses

A number of sensitivity analyses were performed. For the analyses of prevalence, we first restricted the diagnoses to primary diagnoses and second we disregarded admissions up to 90 days before the ovarian cancer diagnosis. For the analyses of incidence, we calculated the HR for the entire follow-up period, the first year only and when excluding already prevalent disease (diagnosed before or up to 30 days after ovarian cancer diagnosis).

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

RESULTS

Population characteristics

In total, 11 139 patients with invasive ovarian cancer were identified. Median age at diagnosis was 63 years and 49% got their ovarian cancer diagnosis at between 50 and 69 years of age. The most common tumour type was high-risk epithelial tumours (76.9%). Table 1 illustrates relative survival according to age, year of diagnosis and histological subtype. The median survival was 653 days for all ovarian cancer patients. Older women had a shorter median survival than younger, more apparent in 5-year than in 1-year survival. Since we only had survival data until 2006, patients

Table 1 Numbers and survival proportion of ovarian cancer by age at diagnosis, time period and histology

	N	(%)	One-year survival (%)		Five-year survival (%)	
All	11139		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 tumour	146	(1.3)	140	(95.9)	130	(89.0)
Stroma cell tumour	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)

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

Epidemiology

diagnosed 2002 and later were not included in the survival analyses. Patients with ovarian sarcomas had the poorest 5-year survival rate (21%); followed by high-risk epithelial and medium-risk epithelial tumours. Patients with germ cell and stroma cell tumours had a high 5-year survival rate of 86–89%.

Analysis of co-morbidity

Table 2 demonstrates the relative prevalence of 13 categories of co-morbidity diagnoses from 10 years before until 30 days after ovarian cancer diagnosis compared with controls. Results indicated that 11 out of 13 of the pre-defined diagnosis groups were more common among ovarian cancer patients than controls. The highest OR for ovarian cancer patients was seen for; haematologic complications (anaemia, neutropenia and thrombocytopenia), with an OR = 3.6 and a prevalence of 4.7% in ovarian cancer patients, thromboembolism (OR = 2.5, 95%, prevalence 3.2%), hypertension (OR = 2.2, prevalence 9.6%) followed by thyroid disease and gastrointestinal (GI) complications (ileus, perforation or GI haemorrhage).

When restricting analyses to primary diagnoses at hospitalisation, four diagnoses had statistically significant higher risk of ovarian cancer compared with controls; thromboembolism (OR = 1.9), haematologic complications (OR = 1.6), GI complications (OR = 1.5) and liver/pancreatic disease (OR = 1.3) (Table 2). When excluding co-morbidity diagnosed within 90 days before the ovarian cancer diagnosis, only the risk of liver and pancreatic disease (OR = 1.4) was statistically significant elevated (Table 2).

Analyses of prevalent co-morbidity in patients with high-risk and medium-risk epithelial tumours compared with controls are presented in Table 3. The results were overall similar between the two histological groups.

Table 4 demonstrates the relative incidence of co-morbidity overall and the HRs for the first year. The highest risk increase among ovarian cancer patients was for haematologic complications, which was most frequent the first year after diagnosis with an HR of 23.4. There were also large risk increases the first year for thromboembolism and GI complications (HR = 14.9 and 9.2, respectively). Excluding prevalent cases had only minor effects on the results.

DISCUSSION

This study is to our knowledge the largest population-based study of co-morbidity among women with ovarian cancer. We detected several increased co-morbidity conditions at time of diagnosis

Table 2 Odds ratios (ORs) and 95% confidence intervals (CIs) of ovarian cancer in association with prevalent co-morbidities in 11 139 ovarian cancer patients and 55 687 controls

	All diagnoses			Only primary diagnosis			Exclusion of prior 90 days[a]		
End points	**Case/control**	**OR**	**95% CI**	**Case/control**	**OR**	**95% CI**	**Case/control**	**OR**	**95% CI**
Haematologic complications	520/750	3.6	(3.2–4.1)	88/281	1.6	(1.2–2)	144/704	1.0	(0.9–1.2)
Thyroid disease	254/605	2.1	(1.8–2.5)	35/152	1.2	(0.8–1.7)	124/567	1.1	(0.9–1.3)
Cardiovascular disease	1027/4344	1.2	(1.1–1.3)	679/3379	1.0	(0.9–1.1)	774/4117	0.9	(0.9–1.0)
Cerebrovascular event	330/1744	0.9	(0.8–1.1)	298/1619	0.9	(0.8–1)	285/1632	0.9	(0.8–1.0)
Thromboembolic events	354/730	2.5	(2.2–2.8)	225/613	1.9	(1.6–2.2)	139/689	1.0	(0.8–1.2)
Hypertension	1074/2728	2.2	(2.2–3.0)	84/388	1.1	(0.9–1.4)	475/2575	0.9	(0.8–1.0)
Pulmonary disease	155/706	1.1	(0.9–1.3)	50/382	0.7	(0.5–0.9)	87/658	0.7	(0.5–0.8)
GI complications	932/2410	2.0	(1.9–2.2)	507/1737	1.5	(1.3–1.6)	460/2325	1.0	(0.9–1.1)
Diabetes mellitus	440/1399	1.6	(1.4–1.8)	113/566	1.0	(0.8–1.2)	245/1329	0.9	(0.8–1.1)
Liver/pancreatic disease	140/465	1.5	(1.3–1.8)	103/385	1.3	(1.1–1.7)	119/440	1.4	(1.1–1.7)
Urinary tract complications	55/157	1.8	(1.3–2.4)	25/80	1.6	(1–2.5)	32/145	1.1	(0.8–1.6)
Infectious complications	694/1901	1.9	(1.7–2.1)	299/1370	1.1	(1–1.2)	589/3207	0.9	(0.8–1.0)
Neoplasms	892/2476	1.9	(1.7–2.0)				331/1801	1.1	(1–1.2)

Abbreviation: GI = gastrointestinal. [a]Exclusion of all primary and secondary diagnoses within 90 days before ovarian cancer diagnosis.

Table 3 Odds ratios (ORs) and confidence intervals (CIs) of ovarian cancer in association with prevalent co-morbidities by histology groups

	High-risk epithelial tumours[a]			Medium-risk epithelial tumours[b]		
	Cases ($n = 8567$)/ controls ($n = 42\,835$)	**OR**	**95% CI**	**Cases (1504)/ controls ($n = 7518$)**	**OR**	**95% CI**
Haematologic complications	388/592	3.4	(3.0–3.9)	66/86	3.9	(2.8–5.4)
Thyroid disease	201/485	2.1	(1.8–2.5)	28/78	1.8	(1.2–2.8)
Cardiovascular disease	818/3498	1.2	(1.1–1.3)	106/494	1.1	(0.9–1.4)
Cerebrovascular event	268/1433	0.9	(0.8–1.1)	44/180	1.2	(0.9–1.7)
Thromboembolic events	267/566	2.4	(2.1–2.8)	58/105	2.9	(2.1–4.0)
Hypertension	862/2206	2.1	(2–2.3)	133/307	2.4	(1.9–2.9)
Pulmonary disease	123/584	1.1	(0.9–1.3)	15/72	1.0	(0.6–1.8)
GI complications	743/1937	2.0	(1.9–2.2)	116/281	2.2	(1.7–2.8)
Diabetes mellitus	343/1143	1.5	(1.4–1.7)	58/143	2.1	(1.5–2.9)
Liver/pancreatic disease	110/363	1.5	(1.2–1.9)	25/65	1.9	(1.2–3.1)
Urinary tract complications	43/124	1.7	(1.2–2.5)	7/19	1.9	(0.8–4.4)
Infectious complications	539/1513	1.8	(1.7–2.0)	83/226	1.9	(1.5–2.5)
Neoplasms	691/1988	1.8	(1.7–2.0)	128/310	2.2	(1.8–2.7)

Abbreviation: GI = gastrointestinal. [a]High-risk epithelial tumours included serous and endometroid adenocarcinomas, anaplastic, small cell and poorly differentiated carcinomas. [b]Medium-risk epithelial tumours included mucinous adenocarcinomas, clear cell carcinomas and mesonefroid cancers.

Table 4 Association between the incidence of co-morbidity in 11 139 ovarian cancer patients and 55 687 controls estimated by hazard ratios (HRs) and confidence intervals (CIs)

	All years of follow-up[a]			First year of follow-up[b]			Excluding prevalent cases[c]		
	Cases/controls	HR	95% CI	Cases/controls	HR	95% CI	Cases/controls	HR	95% CI
Haematologic complications	1253/1384	8.6	(7.9–9.3)	729/186	23.4	(19.9–27.6)	1144/1285	8.8	(8.0–9.5)
Thyroid disease	197/1122	1.8	(1.5–2.0)	93/150	3.7	(2.9–4.8)	129/969	1.4	(1.2–1.7)
Cardiovascular disease	1219/7630	1.6	(1.5–1.7)	536/1495	2.2	(2.0–2.4)	773/5429	1.5	(1.4–1.6)
Cerebrovascular event	357/3156	1.2	(1.1–1.3)	114/442	1.6	(1.3–2.0)	320/2814	1.2	(1.1–1.4)
Thromboembolic events	824/959	7.9	(7.1–8.7)	391/152	14.9	(12.3–18.1)	743/882	7.9	(7.1–8.7)
Hypertension	911/5544	1.7	(1.5–1.8)	100/331	1.8	(1.4–2.2)	514/4530	1.3	(1.2–1.4)
Pulmonary disease	281/1628	1.6	(1.4–1.8)	3/17	1.1	(0.3–3.6)	234/1289	1.9	(1.6–2.1)
GI complications	1938/2436	7.2	(6.8–7.7)	762/486	9.2	(8.2–10.3)	1647/1936	8.2	(7.7–8.8)
Diabetes mellitus	507/2540	1.8	(1.6–2.0)	280/544	3.1	(2.7–3.6)	231/1704	1.4	(1.2–1.6)
Liver/pancreatic disease	99/605	1.6	(1.3–2.0)	32/84	2.3	(1.5–3.4)	89/560	1.6	(1.3–2.0)
Urinary tract complications	207/631	3.3	(2.8–3.9)	75/93	5.0	(3.6–6.8)	193/571	3.6	(3.0–4.2)
Infectious complications	1055/3499	3.0	(2.8–3.2)	459/505	5.4	(4.8–6.2)	959/3114	3.2	(3.0–3.5)
Neoplasms	124/512	2.4	(2.0–2.9)	44/72	3.5	(2.4–5.1)	369/3208	1.5	(1.3–1.6)

Abbreviation: GI = gastrointestinal. [a]End of follow-up was the first date of an admission with the diagnosis of interest, date of death, date of ovarian cancer diagnosis for a control subject, or 31 December 2006, whichever came first. [b]Follow-up started 30 days after cancer diagnosis. [c]The prevalence was defined as having one of the selected diseases either as a primary or as a secondary discharge diagnosis from 10 years before the ovarian cancer diagnosis up to 30 days after.

of ovarian cancer compared with the general population. When disregarding diagnoses within 90 days of cancer diagnosis, the differences of co-morbidities between cancer patients and general population almost disappeared. The increased incidence of haematologic, thromboembolic and GI complication was most pronounced the first year after ovarian cancer diagnosis, whereas risks of the most other diagnosis groups were increased the whole follow-up period.

Abdominal pain, swelling and nausea are the most common symptoms in ovarian cancer (Bankhead *et al*, 2005; Hippisley-Cox and Coupland, 2012) and might mimic GI disease and liver/gall bladder disease which were common diagnoses among the ovarian cancer patients in the present study. Urinary tract symptoms are also frequent at diagnosis of ovarian cancer (Bankhead *et al*, 2005), which was in line with our findings of increased prevalence of such complications close to cancer diagnosis. It is of great clinical importance that the diagnosis of the underlying cancer is not delayed in women with common symptoms from the GI or urinary tract. The prevalence of thromboembolism and anaemia was more than doubled in women later diagnosed with ovarian cancer, which should be bear in mind by the clinician.

Well-known complications in ovarian cancer patients related to treatment and the disease itself are bone marrow suppression, GI problems and thromboembolism. These conditions peaked the first year after diagnosis as expected, but were still significantly increased the following years. This indicates either long-term complications due to treatment or that the cancer itself might cause these problems. In the present study, 11% of the cancer patients developed haematologic complications during the follow-up period, which is a lower frequency than expected (Nurgalieva *et al*, 2010), and must be interpreted as an omission to report these expected findings.

A potential bias in the study was that a cancer diagnosis usually was preceded as well as followed by a period of hospital care due to diagnostic procedures, treatment, symptoms and sometimes complications. The increased probability to detect other conditions (surveillance bias) might influence the comparison with the general population. In this study, we tried to overcome these methodological obstacles by various sensitivity analyses. In the model we disregarded admissions up to 90 days before the ovarian cancer diagnosis, in order to assess the impact of diagnoses being a potential consequence of the ovarian cancer in occult form, or an effect of the increased diagnostic intensity due to the developing ovarian cancer symptoms before registered diagnosis. In the other prevalence analysis model, we included primary diagnoses only in order to include only the most clinically important diagnoses. These two adjustments increased the specificity of diagnosis, although at the price of decreased sensitivity. In the studies of incidence, we excluded all patient with a prevalent co-morbidity diagnosis in order to assess 'true incident' occurrences of a diagnosis (i.e., new cases in previously healthy patients), in order to avoid potential bias of incidences and HRs due to detection of recurring conditions or registration of chronic conditions. These exclusions had no major effects on the results and it should be noted that the start of follow-up was 30 days after cancer diagnosis. Since the risk of developing ovarian cancer and co-morbidity may vary with other factors in life, such as socioeconomic status, parity and ethnicity (Jensen *et al*, 2008; Mousavi *et al*, 2011) these parameters might have a confounding influence on our results. In this large study population, we did not have access to all this information; however, our results show that the spectrum of diseases between groups was similar >3 months before diagnoses and this speaks against a major bias.

We did not have access to data on FIGO stage of the diagnosed cancer. To approximate the influence of the malignant potential of the ovarian cancer, we performed subgroup analyses according to histological subtype in epithelial tumours. The tumour type in the medium-risk group (mucinous adenocarcinomas, clear cell carcinomas and mesonefroid cancers) is more often diagnosed in an early stage than the high-risk tumours (seropapillar, endometroid and poorly differentiated tumours) (Bjorge *et al*, 1998). Although the differences between the histological types were minor, the prevalence of cardiovascular disease and urinary tract complications was significantly increased in patients with high-risk tumours only.

The Swedish Patient Register does not historically include diagnoses from outpatient care during the study period. This might lead to underestimation of not emergent conditions, such as hypertension, thyroid disease and diabetes in the control group and might explain the increased prevalence of these conditions close to cancer diagnosis. However, diagnosing of these conditions earlier than 3 months before cancer diagnosis should not differ between cancer cases and controls. Patients with acute conditions such as thrombosis and cerebrovascular events are most likely to be hospitalised and are therefore less likely to introduce bias.

An association between hypertension or alternatively hypertensive drugs and cancer, including ovarian cancer, has previously been found (Peeters *et al*, 1998; Grossman *et al*, 2002; Assimes and Suissa, 2009; Largent *et al*, 2010). In addition, diabetes mellitus has been suggested as a risk factor for ovarian cancer as well as other cancers (Swerdlow *et al*, 2005; Inoue *et al*, 2006; Hemminki *et al*, 2010).

We saw an increased prevalence of hypertension as well as diabetes mellitus in women developing ovarian cancer, but the differences disappeared when disregarding the period of 90 days before cancer diagnosis. The same pattern was seen for cardiovascular disease, thyroid disease and infections. When measuring incidence of co-morbidity from cancer diagnosis and forward, the pattern was slightly different with an increased risk of most internal medicine diagnoses studied among cancer patients. Whether this risk increase is associated with the disease or the treatment cannot be resolved in this study, but it is of clinical importance since it contributes to mortality and morbidity in cancer patients (van de Poll-Franse *et al*, 2007; Stewart *et al*, 2010).

CONCLUSION

Our study illustrates the essentiality of defining co-morbidity related to time window around the cancer diagnosis. Our results indicate that women developing ovarian cancer do not have higher overall morbidity than other women earlier than 3 months preceding cancer diagnosis. However, at time of diagnosis 11 of 13 prevalent diagnosis groups were more common among ovarian cancer patients, but this might be influenced by surveillance bias or early cancer symptoms. The incidence of many common diagnoses as well as other cancers was increased several years following the ovarian cancer.

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APPENDIX

Table A1 Definition of co-morbidity subgroups (ICD-codes)

	ICD-9	ICD-10
Haematologic complications		
Anaemia	280, 2822, 2830–2832, 2839, 2840, 2848, 2850, 2851, 2858, 2859	D50, D59, D61, D62, D63, D640–D643
Neutroleucopenia	2792, 2880, 2882, 2883, 2888, 2889	D70, D72
Myelodysplastic syndrome	2849, 2850, 2888	D46
Thrombocytopenia	2862–2865, 2867, 2869, 2873–2875	D68, D693–D696
Thyroid disease		
Hyperthyroidism	242	E05
Hypothyroidism	2443, 2449	E032, E039

Epidemiology

Table A1 *(Continued)*

	ICD-9	ICD-10
Cardiovascular disease		
Cardiac dysrhythmias	427	I460, I469, I47–I49
Coronary artery disease	410–414	I20–I22, I24–I25
Heart failure	514, 428, 5184	I50, J81
Myocardial infarction	410, 412	I21–I22, I252
Cerebrovascular event		
CNS haemorrhages	430–432	I60–I62
Cerebrovascular accident	433–435	G45, I63, I65–I66
Thromboembolic events		
Deep vein thrombosis	4511–4512, 4518, 452–453	I801–I803, I808, I81–I82
Pulmonary embolism	4151	I269
Hypertension		
Hypertension	401, 4020, 4021, 4029, 4030, 4031, 4039, 4040, 4041, 4049, 405	I10–I13, I15
Pulmonary disease		
Interstitial lung disease, narrow	515–516	J84
Interstitial lung disease, broad	4959, 501–505, 5060, 5064, 5081, 5088, 515–516, 5172, 5178, 5183	J61–J64, J66, J679, J680, J684, J701–J704, J708, J82, J84, J991
ILD, spec. idiopathic fibrosing alveolitis	5163	J841
Chronic obstructive pulmonary disease	4789, 4910, 4911, 4912, 4918, 4919, 492, 496	J41–J44
Respiratory insufficiency	4787, 5070, 514, 5183, 5184, 5185, 5190, 7991, 9973	J80, J81, J95, J96
GI complications		
Fistula, GI	5374, 5651, 5751, 5755, 5764, 5961, 5439, 5698	K316, N321, K383, K603–K605, K633, K823, K833
GI-haemorrhage, lower	5620–5621, 578	K57, K920–K922
GI haemorrhage, upper	5302, 5310, 5312, 5314, 5316, 5320, 5322, 5324, 5326, 5330, 5332, 5334, 5336, 5340, 5342, 5344, 5346, 5780	K250, K252, K254, K256, K260, K262, K264, K266, K221, K270, K272, K274, K276, K280, K282, K284, K286, K228, K520–K522
GI perforation, oesophagus	5304, 2500–2507, 2509, 2510	E14, K223
GI perforation, intestine	5400, 5671, 5672, 5679, 5678, 5688, 5698, 5778, 5733	K631, K65
Paralytic ileus, intestinal obstruction	560	K56
Diabetes mellitus		
Diabetes mellitus	250	E10–E11
Liver/pancreatic disease		
Liver disease, biliary	575–576	K81–K83
Liver disease, hepatitis	570, 5733	K720, K71
Pancreatitis	5770–5771	K85, K860–K861
Urinary tract complications		
Fistula genitourinary	5962, 5991, 619	N322, N360, N82
Renal failure	584–586	N17–N19
Proteinuria	7910, 5936	R80, N06
Infectious complications		
Sepsis	038	A40–A41
Pneumoni	481–483, 485–486	J13, J15, J16, J18
Pyelonefrit	5901	N10
Wound healing	9981, 9983	T810, T813
Neoplasms		
Neoplasms	140–182, 184–239	C00–C55, C57–D48

Abbreviation: GI = gastrointestinal.