Prognosis for ovarian cancer in Denmark 1980-2005:

Studies of use of hospital discharge data to monitor and study prognosis and impact of comorbidity and venous thromboembolism on survival

PhD thesis

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Preface

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Contents

Abbreviations

CA-125	Tumour marker – cancer antigen 125
CI	Confidence interval
DCR	Danish Cancer Registry
ECOG	Eastern Cooperative Oncology Group
FIGO	International Federation of Gynecology and Obstetrics
HDR	Hospital Discharge Registry
ICD	International Classification of Diseases
MRR	Mortality rate ratio
PP	Prevalence proportion
PPV	Positive predictive value
RMI	Risk of malignancy index
SIR	Standardized incidence rate
VTE	Venous thromboembolism
WHO	World Health Organisation
WSP	World standard population

1 Introduction

With 600 new cases diagnosed annually, ovarian cancer is the sixth most common cancer among women in Denmark (1). The incidence rate of ovarian cancer increases with age, with more than 50% of newly diagnosed cases occurring in women aged 60 years or older. The change in population demographics caused by improved life-expectancy (2) will result in an increased proportion of ovarian cancer patients with coexisting diseases (comorbidity). Likewise, the incidence of ovarian cancer itself is expected to increase and remain a burden in the future.

Ovarian cancer has a poor prognosis (5-year relative survival 32%) (1), which is worse in Denmark than in other countries (3). Ovarian cancer has been described as a "silent killer" because the majority of patients present with symptoms only after the disease has spread outside of the ovary and sometimes outside of the pelvis. Thus, approximately two-thirds of patients with ovarian cancer present with tumour stage III or IV according to the classification of International Federation of Gynecology and Obstetrics (FIGO) (4). Furthermore, approximately 60% of ovarian cancers tend to recur, even in patients who achieve a complete response to primary treatment (5).
Comorbidity, which is often present in elderly cancer patients (6), may affect survival after ovarian cancer. Venous thromboembolism (VTE), as a first symptom of cancer, is strongly associated with ovarian cancer (7), and may likewise affect survival.
In order to ensure quality of ovarian cancer care, quality assurance systems must be in place to monitor effectiveness of therapeutic outcomes with updated data. Further, to improve survival after ovarian cancer, we need better understanding of the disease. This includes investigating prognostic factors, as VTE and comorbidity, with the aim of developing targeted interventions.

In this thesis I used population-based registries to examine: 1) the quality of the ovarian cancer diagnosis in the updated regional hospital discharge registry, 2) ovarian cancer survival from 1985 to 2004, 3) the impact of prior VTE on survival, and 4) the impact of comorbidity on ovarian cancer survival, while accounting for tumour stage.

1.1 The burden of ovarian cancer

There is a marked international variation in the incidence rates of ovarian cancer (see Table I). In Denmark, its incidence remained relatively stable in recent decades. However, with

approximately 13.7 new cases per 100,000 women diagnosed annually (age-standardized, WSP) (8), Denmark has one of the highest incidence rates of ovarian cancer (4;9).

Table I. Incidence in selected countries

Country	Annual incidence
Denmark(1)	13.7 per 100,000 women (age-standardized, WSP)
Norway(10)	13.2 per 100,000 women (age-adjusted, 2000)
Sweden(11)	12.6 per 100,000 women (age-standardized, WSP)
Northern Europe(12)	13.3 per 100,000 women (age-standardized, WSP)
Western Europe(12)	11.3 per 100,000 women (age-standardized, WSP)
Eastern Europe(12)	10.2 per 100,000 women (age-standardized, WSP)
Southern Europe(12)	9.7 per 100,000 women (age-standardized, WSP)
USA(9)	9.0 per 100,000 women (age-adjusted, US 2000 population)

1.2 Risk factors

Since causes of ovarian cancer are largely unknown (13), prospects of its prevention remain elusive, bringing in the focus optimised diagnostics and treatment. Reproductive factors, notably, higher parity, oral contraceptive use and tubal ligation have a protective effect against ovarian cancer (14). Some studies have also reported reduced risk of invasive ovarian tumours among women with late pregnancies (15;16). Use of infertility drugs may be associated with an increased risk of ovarian cancer, however, a causal relation has not been shown (17;18).

A family history of ovarian cancer is a strong risk factor (14;19), with hereditary disease accounting for 3-5% of cases (13). Three autosomal dominant syndromes have been identified: hereditary breast and ovarian cancer, hereditary site-specific ovarian cancer, and hereditary non-polyposis colorectal cancer (the Lynch II syndrome) (13).

1.3 Quality of ovarian cancer care

Quality assurance systems and ongoing monitoring are needed to be in place in order to ensure quality of ovarian cancer care (20). Medical databases can be used for this purpose. The aims of quality assurance are to compare practice with evidence-based medicine; define guidelines; measure proportion of treatments carried out in accordance with guidelines; construct a method to close the gap between evidence-based guidelines and the actual treatment of patients; define intermediary measurable variables; and re-evaluate results.

Continuously available data on survival may be an important tool for improving survival after ovarian cancer treatment by modifying therapeutic strategies to include those with the best-demonstrated effectiveness (20). Access to quality assurance systems based on up-to-date data sources is a potentially important tool for the physicians in their daily clinical work (20;21).
Quality assurance systems may be linked to quality registries, but several requirements must be fulfilled (Box 1).

Box 1 Requirements of a monitor system

- Continuous registration
- Valid data
- Availability of data
- Inclusion of relevant clinical end-points
- Complete data of adequate quality
- Regional availability of the data
- Feedback system
- Inclusion in clinical practice
- Availability of relevant explanatory variables (e.g. emergency hospitalisation, diagnosis, time, etc.)

In Denmark, ovarian cancer cases are primarily registered in the Danish Cancer Registry (DCR), in a clinical database (DGCD), and in the Hospital Discharge Registry. These population-based registries and the database have different advantages and disadvantages, which should be considered in order to evaluate the feasibility of their use in monitoring ovarian cancer care.

The DCR is a high-quality registry (22), but the by-product of the high data completeness is delay in data availability, resulting in available data being 3-4 years old. Furthermore, the DCR registers only the month and the year of diagnosis, has some missing data on tumour stage, registers only treatment given within the first four months after the diagnosis, does not provide the exact date of treatment administration, and has no data on comorbidity or complications.

Problems with clinical databases based on primary data collection include incomplete registration of patients and missing data. Clinical databases, as DGCD (Danish Gynecological Cancer Database), may be of high quality. Data is collected at the local hospital in the depart-

ments of gynecology, pathology and oncology and include detailed information on treatment, pathology and complications. Data is registered online and transferred to the national database at the "Rigshospitalet" in Copenhagen. However, the database is newly established (2005), implying that long-term effects cannot be measured. Further, a certain delay in data availability may be present and the completeness of the database has of yet not been published.

Using the regional Hospital Discharge Registry (HDR) to monitor ovarian cancer survival has several advantages, including availability of:

- Data on departmental level
- Data on admission and discharge
- Data on comorbidity
- Data on surgery type, e.g. acute, elective
- Data on complications
- Data on radiotherapy and chemotherapy
- Up-to-date and complete information

A disadvantage of this source is incompleteness of information on the stage of ovarian cancer. In the period 1998-2000, 15% of all Danish ovarian cancer patients, who were admitted to a department of gynecology and operated on, were coded with an unspecified stage (department range 0-54%) (23). Moreover, the quality of ovarian cancer diagnosis in the regional HDR for monitoring survival of ovarian cancer has not been validated.

1.4 Concepts of prognosis

1.4.1 Prognosis

Prognosis is a prediction of the outcome of a disease (24), or an explanation of the outcome of the disease, whereas prognostic factors are variables predictive of or explaining future events (25). Survival or mortality is often used as a measure of clinical quality.

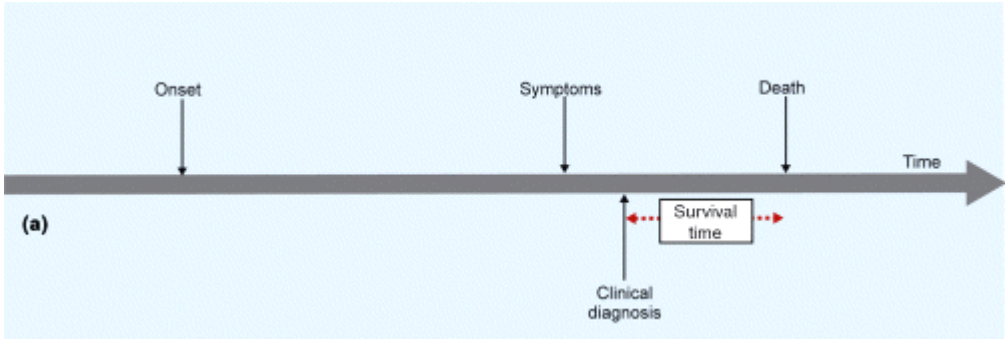
The main purposes of different studies of prognostic factors are shown in Box 2.

Box 2 Purposes of studies of prognostic factors (adapted from Altman and Lyman) (25)

- To guide clinical decision-making, including treatment selection and patient counselling
- To improve understanding of the disease process
- To improve the design and analysis of clinical trials (for example, risk stratification)
- To assist in comparing outcome between treatment groups in non-randomised studies by allowing adjustment for case mix
- To define risk groups based on prognosis
- To predict disease outcome more accurately or parsimoniously

Ovarian cancer progresses from its biologic onset to the time of diagnosis, and ultimately to the outcome (26) (Figure 1). The natural cause of ovarian cancer is defined as the biological progression of the cancer without medical intervention, whereas the clinical course of ovarian cancer is the evolution of the cancer after diagnosis and medical treatment (24).

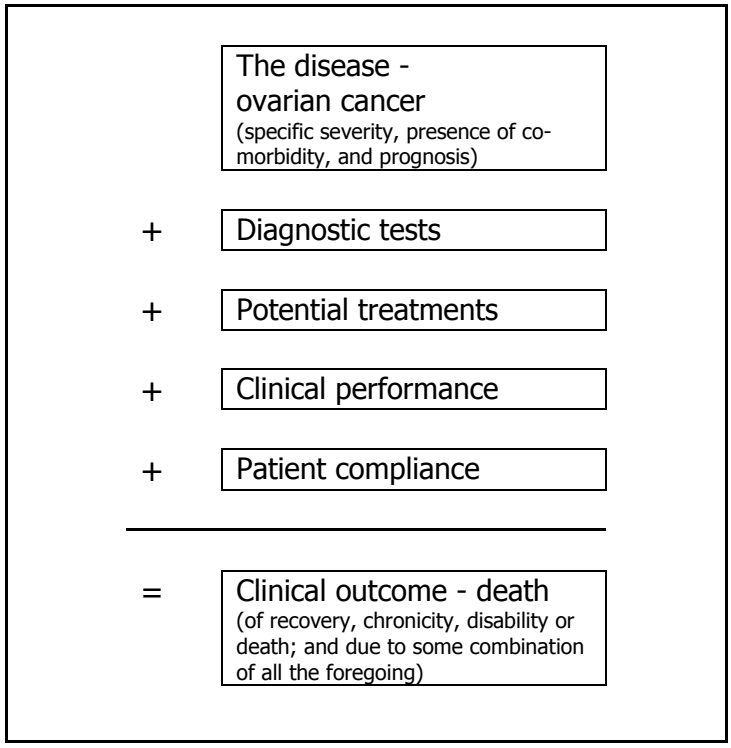
Figure 1 (27)



The prognosis depends on the clinical course of ovarian cancer, including presence of other conditions interacting with the ovarian cancer (as comorbidity or age), potential treatments, clinical performance and patient compliance (26) (Figure 2).

Ovarian cancer may have a long clinical course. Therefore, in order to describe prognosis, we used one-year or five-year survival, which refer to the proportion of ovarian cancer patients surviving one or five years after the diagnosis (24).

Figure 2. The determinants of the outcome of a disease (26)



1.4.2 The index disease – ovarian cancer

Study of the prognostic factors of the index disease can be related to characteristics of the tumour or those of the woman diagnosed with ovarian cancer.

Most consistently reported tumour-related prognostic factors (28;29)

- Degree of tumour invasiveness (for epithelial tumours)
- Stage
- Size of post-surgical residual tumour mass

Ovarian tumours are classified as epithelial tumours, which constitute approximately 90% of all cases, or as tumours of germ or stroma cells (30), which are associated with a better prognosis than epithelial tumours (31). The epithelial tumours may be classified as either malignant (invasive) or borderline, the latter accounting for up to 15% of ovarian tumours (32). Borderline tumours are also called low malignant potential ovarian tumours; they are usually classified as ovarian cancer because they may show signs of malignancy, may be in an advanced stage, may need post-operative chemotherapy and may recur (32). Borderline tumours also differ from invasive tumours in that they tend to occur at a younger age (mean 40 years), and the majority of patients present with an early-stage disease (32). The prog-

nosis of borderline tumours is generally more favourable than that of invasive tumours. In Norway in the 1990's, the 5-year survival was 93% for borderline tumours and 37% for invasive tumours (33). Thus, the estimated survival after ovarian cancer is likely to be higher if borderline tumours are included than if they are excluded. Since there is a different tradition in different countries for coding borderline tumours, the interpretation of prognostic studies is difficult and may cause problems when comparing the existing studies.

Tumour stage is a consistent prognostic factor for ovarian cancer patients (28;34). The most commonly utilised staging system is the FIGO system modified in 1988. The extent of tumour spread at the time of diagnosis is usually classified into FIGO-stage I to IV (35), or unknown. A more favourable stage distribution in younger versus older patients has been reported, which could explain some of the differences in prognosis among age groups (see below) (36;37). No recent trend of an improved stage distribution over time was observed (38), which is not surprising because early detection of the ovarian cancer is difficult. In the HDR ovarian cancer is one of the few cancers where a stage specific code is possible. However, the unspecific ovarian cancer code (C56.9) is often used (23), leading to problems with obtaining sufficient information on stage.

A maximal cytoreduction during the primary surgery has been reported to be the most important prognostic factor in ovarian cancer survival (39;40). However, the behaviour of the tumour may influence the possibility of maximal cytoreduction, hindering optimal surgical debulking.

The most consistently reported host-related prognostic factors are (29)

- Age
- Performance status

Age was shown to be a prognostic factor in several studies (28;41-43). For example, age was a prognostic factor in a European study by Gatta et al. (42). The 5-year relative survival decreased with age, from 64% to 18%, from the youngest (15-44 years) to the oldest (75-99 years) age group (42).

The performance status is a quantitative measure of how well a patient is able to perform ordinary tasks and carry out daily activities. This measure is used to determine whether a patient can receive chemotherapy, whether dose adjustment is necessary, and as a measure

for the required intensity of palliative care. An example is the ECOG (Eastern Cooperative Oncology Group) score (44), also called the WHO (World Health Organization) score, that runs from 0 to 5, with 0 denoting perfect health and 5 death. Some studies have shown performance status to be an independent prognostic factor in ovarian cancer (34;40;45).
In studying its prognosis, ovarian cancer is considered to be the index disease, while other diseases are considered comorbidities. Complications on the other hand, are consequences of the ovarian cancer. A complication of ovarian cancer could be a seemingly unprovoked VTE discovered before the diagnosis of ovarian cancer. VTE and comorbidity can both have a prognostic value in ovarian cancer patients.

VTE – as complication

Venous thromboembolism (VTE) includes deep venous thromboembolism and pulmonary embolism (PE). During deep venous thromboembolism blood clots are formed in the veins, usually those of the leg or the pelvis, but clots can also appear elsewhere. Fragments of such vein clots may break off and travel to the lungs resulting in PE, which is a serious complication with a high mortality (46).

The association between cancer and thromboembolism was first described by Trousseau in 1865 (47). Since then studies have shown that thromboembolic complications in patients with cancer are common, and other circumstantial factors, such as surgery, chemotherapy and use of central venous catheters may enhance this risk (48-54). It has also been shown that patients with VTE have a higher risk of being diagnosed with cancer (7;55). Risk of being diagnosed with ovarian cancer has been strongly associated with VTE (7;55;56). However, information on the prognosis of ovarian cancer patients with prior VTE is sparse.

Comorbidity

Comorbidity was described by Last as "disease(s) that coexist(s) in a study participant in addition to the index condition that is the subject of study" (57). According to Feinstein, comorbidity is "any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study" (58). In ovarian cancer patients, comorbidity may cause a delay in diagnosis, allowing tumours to progress to advanced stages; influence prognosis of ovarian cancer or choice of therapy; and confound associations in studies. Thus, comorbidity is an important consideration for patient care and for research (59;60).

The incidence of ovarian cancer increases sharply with age, as does the prevalence of co-morbid diseases (61;62). A study of a Dutch cancer registry reported that the prevalence of comorbidity among incident cancer patients ranged from 12% among patients younger than 45 years to 63% among patients who were 75 years or older (6).

There is a variety of methods to measure comorbidity (63), some of them being a simple count of the existing diseases and others using severity-weighted indices. Study population and outcome determine the choice of comorbidity measure (63;64).

The Charlson Comorbidity Index is the method most frequently used to measure comorbidity. It was developed by Mary Charlson (65) at the Cornell Medical Center, in New York. During a one-month period in 1984 all patients admitted to the medical service (n=559) were evaluated on admission, and all comorbid diseases were recorded. One-year follow-up was obtained for these patients, and the prognostic impact of individual comorbid diseases was evaluated. The diseases were then categorized into 19 distinct medical conditions and a weighted index was created that accounted for the number and the seriousness of comorbid diseases (65). The Charlson Comorbidity Index was subsequently validated in a cohort of 685 breast cancer patients. After ten years of follow-up, comorbidity as measured by the Charlson Index was found to be a reliable predictor of death (65).

The Charlson Comorbidity index has been used in a variety of database studies of cancer (66-69). For example in a study among women with breast cancer by West et al. the 10-year mortality rate ratios (MRR) were 1.23, 2.58, and 3.44 for Charlson Comorbidity Index 1, 2, and 3+, respectively (69). The index is capable to predict mortality for periods ranging from few weeks up to 10 years among different patient populations, including persons with cancer (69;70).
There is a potential to misclassify comorbidity when administrative data are used to ascertain diagnoses (71). Charlson Index has high specificity (63), but a variable degree of sensitivity (72), when the information is compared with medical records.

1.4.3 Diagnostic tests: The diagnostic test refers to both the process of detection of ovarian cancer and to the result of such process (57).
The symptoms of ovarian cancer are often vague and non-specific. In Denmark, a preoperative risk score RMI (risk of malignancy index) is used in the evaluation of patients with adnexal masses to identify possible ovarian cancer patients. The definitive diagnosis of ovar-

ian cancer, however, requires a surgical specimen. RMI is based on menopausal status, ultrasonographic findings, and serum CA-125 level, and has a sensitivity of 71% and specificity of 92% (73;74). In the 1980's, preoperative ultrasonography and serum CA-125 levels were introduced as predictors for ovarian cancer (75). Using ultrasonography and serum CA-125, attempts have been made to detect ovarian cancer early by screening asymptomatic women, but no satisfactory screening method has yet been developed. Since screening for ovarian cancer to detect the disease in an earlier stage is not available, currently optimising treatment seems to be the best strategy to improve survival. In order to optimise the treatment it is important to understand the impact on survival of patient characteristics, such as age or comorbidity.

When diagnosing ovarian cancer staging is important in order to offer the patients the best treatment. FIGO staging is based on findings made mainly through surgical exploration, therefore adequate surgical performance is essential for correct staging of ovarian tumours (76).

1.4.4 Treatments: According to the international (76) and Danish national guidelines (77), the two most important elements of treating ovarian cancer (primary epithelial tumours), depending on stage, are surgery and chemotherapy. Tumours in FIGO stage Ia-Ib (well differentiated and non-clear-cell histology) have a good prognosis and do not require adjuvant chemotherapy; whereas other FIGO stage I and all FIGO stage II-IV cases generally are treated with chemotherapy after surgery. Improved and more aggressive treatment of ovarian cancer available since 1980's may partially explain the improvement in survival. The most important factor affecting the survival positively is a maximal cytoreduction during the primary surgery (39). Use of platinum-based chemotherapy, since 1980, has improved prognosis (78-80), and the introduction, in the mid-1990's, of paclitaxel may have further prolonged the expected survival (81;82). In some cases patients are treated with chemotherapy and only have surgery for diagnostic purpose. Adjuvant radiotherapy for ovarian cancer has not been used as a standard treatment in Denmark since 1988 (personal communication, Dr. Søgaard Andersen), but some ovarian cancer patients may receive radiotherapy. In patients considered unsuitable for aggressive surgery and chemotherapy (because of age or comorbidity), hormonal or anti-hormonal therapy can be considered as palliative treatment.

1.4.5 Clinical performance: Clinical performance refers to clinical competence and motivation of the gynaecologist treating the ovarian cancer patient, but is also related to overcoming any barriers (26).

Often it is the gynaecologist's training and experience that influences the choice of treatment, its aggressiveness, and extent. In the recent years several international studies have found that the outcomes of ovarian cancer treatment were better when provided by gynaecologic oncologists and in specialized hospitals (83). The gynaecologists' may have barriers related to the choice of treatment of ovarian cancer patients. Old age and presence of co-morbidity in the ovarian cancer patients are probably the most important reasons for the gynaecologists' to withhold surgical therapy in these patients. Since Denmark has not centralized the ovarian cancer treatment, the need for monitoring the clinical performance is important.

1.4.6 Patient compliance: The patient has to cooperate and accept the treatment offered by the physician and surgeon in order to have the best result. Some elderly patients may insist that they have "lived their lives" and should be allowed to die; these patients may be difficult to convince that the treatment is in their best interest. However, in the future the elderly may be better educated, expect greater participation in choosing their treatment, and be less likely to postpone entry into the medical care system (84). The patient compliance of ovarian cancer patients, has to our knowledge, not been studied.

1.5 Existing studies on prognosis

1.5.1 Ovarian cancer and survival

Mortality after ovarian cancer has been extensively studied. We searched the PubMed database (June 5 2007) for English-language studies examining changes in survival over time, using the terms "ovarian cancer" and "survival" and "trends". This search strategy yielded 111 studies. We also searched the PubMed database using the terms "ovarian cancer" and "survival" and "Denmark" or "Scandinavia" to ensure the inclusion of all Danish and Scandinavian studies on the topic. This search, limited to English-language articles, yielded 34 and 76 studies, respectively. Several studies were found by all three search strategies. Additional studies were identified by manual search. Except for Danish studies, we included studies with 5-year survival estimates and excluded reviews. The main results of the selected studies are shown Table IIa and Table IIb.

Few Danish studies described the changes in survival of ovarian cancer over time (4;85-87). Using data from the Danish Cancer Registry, Kjær et al. studied survival after ovarian cancer among patients diagnosed from 1943 to 1987 and found a 5-year survival of 22% among patients diagnosed in 1943-1947. The survival increased over time: among patients diagnosed in 1983-1987 the 5-year survival was 30% (85). No change in survival was seen in the smaller cohort study by Bertelsen et al. comparing periods 1972-1978 and 1981-1986 (86). Ewertz et al. used the Danish Cancer Registry and the national mortality statistics to examine trends in ovarian cancer mortality and found no substantial change in the age-standardized (WSP) average annual mortality rate during the study period (10.5 per 100,000 women in 1953-57 vs. 10.8 per 100,000 women in 1978-82); peak annual mortality was found in the period 1968-1972 (12.1 per 100,000 women) (87). A more recent Danish population-based study (4) did report a decline in mortality (Table IIa). Similarly, the survival increased over time in other Nordic countries (33;88-90), but the survival was consistently better in the other Nordic countries than in Denmark. Improvement in survival over time was also reported in Europe, US, and Australia (Table IIb), and even though the studies often excluded borderline tumours, their reported survival was still better than that in Denmark.

1.5.2 VTE and ovarian cancer prognosis

Occasionally, VTE occurs prior to cancer diagnosis, and research suggests that it may be caused by an underlying undiagnosed cancer (91;92). Patients with VTE have a substantially increased risk of ovarian cancer in the months following the episode of VTE (7;55;56). However, little epidemiological information exists on the prognosis of ovarian cancer in patients with preceding VTE. We searched the PubMed database using the terms "ovarian cancer",

"venous thromboembolism", and "prognosis". This search strategy yielded 3 studies. One additional study was identified through communication with other researchers. Only one of the studies examined the prognosis of different cancer patients who had cancer diagnosed at the same time as VTE (668 patients, including 35 ovarian cancer patients), within one year after an episode of VTE (560 patients, including 27 ovarian cancer patients), or more than one year after an episode of VTE (1,906 patients, including 28 ovarian cancer patients) (93). For patients who had cancer diagnosed at the same time as VTE the MRR was 2.46 (95% CI, 2.25-2.68) for the first year of follow-up, and for patients who had cancer diagnosed within one year after an episode of VTE the MRR was 1.35 (95% CI, 1.20-1.50) for the first year of follow-up, all compared with patients who had cancer but not VTE. The study did not examine the prognosis for individual cancer sites.

To the best of our knowledge, no study to date has addressed prognosis among ovarian cancer patients with a prior episode of VTE in a hospital system.

1.5.3 Comorbidity and ovarian cancer prognosis

Few population-based studies have examined the impact of comorbidity on prognosis of ovarian cancer. We searched PubMed (June 5 2007) using the terms "ovarian cancer" and "comorbidity", limiting the search to English-language articles. This search strategy yielded 51 studies, only few (n=6) of which estimated the impact of comorbidity on prognosis of ovarian cancer. An additional study was identified using manual search. We included studies with comorbidity as prognostic variable, but not studies that examined the prognostic impact of a single comorbid condition as, for example, overweight (94). All selected studies were cohort studies and their main results are summarised in Table III. Two studies found a negative prognostic impact of comorbidity on mortality (95;96): an American study, restricted to ovarian cancer patients with FIGO stage IC or higher who were surgically treated and had survived more than 12 days from the time of surgery (95); and a German study, which included one-third of all patients diagnosed with ovarian cancer (all stages) in the third quarter of 2001 in Germany (n=476) (96). In that study, high-volume hospitals, with rigorous quality assurance procedures may have been more likely to participate. Another American study found negative prognostic impact of comorbidity on mortality for gynaecologic cancers, but did not provide specific estimates for ovarian cancer (97). Four studies found no association between comorbidity and mortality (28;98-100) (one of the studies did find comorbidity to be a prognostic factor in the univariate analysis, but this association disappeared in the multivariate analysis (28)). The hospital-based study by DiSilvestro et al. (98) was based a on small number of patients (n=137), and the population-based study by Maas et al. only re-

ported mortality estimates for ovarian cancer in FIGO stage II and III (99). None of the existing studies was carried out in a large group of ovarian cancer patients (all stages and histological types) in a population-based setting.

Table IIa. Danish studies of ovarian cancer survival and mortality								
Authors	**Country**	**Study period**	**Design**	**Number**	**In- or exclusions**	**Adjustment**	**Risk estimates**	**Results**
Denmark								
Kjær et al. (85)	Denmark	1943-1987	Cohort	19,476 women	<90 years Excluded: cases identified though autopsy	No	Relative 1 and 5 yrs survival	Rel. 1 yr survival: 1943-47: 40% 1983-87: 61% Rel. 5 yr survival: 1943-47: 22% 1983-87: 30%
Bertelsen et al. (86)	Denmark	1973-1992	Cohort	206 women in 1973-78, and 206 women in 1981-86	Epithelial no borderline Excluded: cases identified though autopsy	No	5 yr survival	5 yr survival: 1973-78: 27.5% 1981-86: 26.7%
Kjærbye-Thygesen et al. (4)	Denmark	1978-2002	Cohort	14,325 women	All types of ovarian cancer	No	Mortality rates	1978-82: 10.8 per 100,000 person yrs 1998-99: 9.0 per 100,000 person yrs
Ewertz et al. (87)	Denmark	1943-1982	Cohort	17,956 women	All types of ovarian, fallopian, and broad ligament cancer.	Age standardized (WSP)	Mortality rates	1953-57: 10.5 per 100,000 person yrs 1978-82: 10.7 per 100,000 person yrs
Table IIb. Studies of ovarian cancer survival with 5-year survival estimates								
The Nordic countries								
Granberg et al. (88)	Sweden	1969-1972 1979-1982	Cohort Hospital-based	172 women 179 women	FIGO I and II No borderline Patients with death of non ovarian cancer causes excluded	No	None	1969-72: 92 out of 161 are alive after 5 years 1979-82: 113 out of 170 are alive after 5 years.
Høgberg et al. (101)	Sweden	1984-1992	Cohort Population-based	407	Excluded: cases identified though autopsy	Relative Cause specific	5 yr survival	1984-87: 5 year survival 43%
Åkeson et al. (89)	Sweden	1993-1998	Cohort	Regional registry (GC) 718	Epithelial Excluded: cases identified though autopsy	Relative	5 yr relative survival	5 yr relative survival Western health care region 1988-93: 42.1% 1993-98: 45.4% The rest of Sweden: 1988-93: 38.2% 1993-98: 41.8% Sweden GC- regional:

								1993-98: 46.1%
Bjørge et al. (33)	Norway	1954-1996	Cohort Population-based	14,160	<90 yrs Excluded: cases identified though autopsy	Age	5 yr age adj. relative survival	5 year age adj. rel. survival 1954-58: 22% 1989-93: 37%
Bjørge et al. (90)	Norway	1975-1996	Historical cohort Hospital-based	2,769	Epithelial Excluded: cases identified though autopsy, borderline, clinical diagnosis	Age	5 yr age-adj. survival	5 year age adj. survival 1975-79: 39% 1990-94: 43%
Tingulstad et al. (28)	Norway	1987-2002	Cohort Population-based	571	no borderline Excluded: cases identified though autopsy	No	5 yr survival	1987-96: Crude 5 yr survival: 39% Disease specific 5 yr survival: 41%
Kumpulainen et al. (102)	Finland	1983-1999	Cohort Population-based	3,851	No borderline Excluded: cases identified though autopsy, no surgery	No Stratified by type of hospital	5 yr relative survival	1983-94: 5 yr rel. survival: University: 45% Central: 37% Other: 45%
Europe								
Gatta et al. (42)	Europe	1978-1994	Cohort Based on cancer registries in 17 European countries (EUROCARE II database)	DK: 2,932 Europe: 29,107	no borderline Excluded: cases identified though autopsy	Age standardized	5 yr survival	5 yr survival (DK): 1978-80: 24.4% 1987-89: 30.5% 5 yr survival (Europe): 1978-80: 28.9% 1987-89: 32.2%
Sant et al. (3)	Europe	1990-1998	Cohort Based on cancer registries in 22 European countries (EUROCARE III database)	DK: 2,589 Europe: 43,543		Age, relative survival	5 yr age adjusted relative survival	1990-94: 5 yr age adj. rel. survival DK: 30.9% Europe: 36.7%
Engel et al. (103)	Germany	1978-2000	Cohort Population-based	3,750		Relative	5 yr overall survival	5 yr survival: 1978-87: 40.8% 1988-97: 45.7% 5 yr rel. survival: 1978-87: 42.9% 1988-97: 49.0%
Brenner et al. (104)	Germany	1976-1996	Cohort Population-based	2,124	<80 years no borderline Excluded: cases identified though autopsy	Age stratified	5 yr relative survival using period analysis	5 yr rel survival: <55 yr: 1976-80: 36.6% 1991-95 60.1% 55-64 yrs: 1976-80: 23.7% 1991-95 42.9% <79 yr: 1976-80: 28.8%

								1991-95 39.4%
Gondos et al. (105)	Germany	1979-2003	Cohort	2,260	>15 years Excluded: cases identified though autopsy or death certificate only	Age	5 yr relative survival using period analysis	5 yr rel. survival: 1979-83: 31.2% 1999-03: 45.2%
Balvert-Locht et al. (106)	The Nether-lands	1975-1988	Cohort Population-based	568	No borderline	Relative	5 yr rel. survival	5 yr rel. survival The entire period: 1975-85: 35% 1975-80: 28% 1981-85: 42%
Levi et al. (107)	Switzerland	1974-1990	Cohort Population-based	649	No borderline	Stratified on type and age Relative survival	2 and 5 yr sur-vival	5 yr rel. survival: 1974-81: 28% 1982-88: 36% <60 yr: 45% >=60 yr: 24%
Brun et al. (108)	France	1975-1998	Cohort Hospital-based	287	No borderline	Age stratified	2 and 5 yr sur-vival	1975-95: 5 yr survival <40 yr: 74% 40-60 yr: 39% >60 yr: 21%
Minelli et al. (109)	Italy	1) 1978-1998 2) 1994-2002	Cohort 1) survey 2) cancer registry	1) 217 2) 446	No identified by death certificate only	relative	1- 3- 5-yr sur-vival	5 yr rel. survival 1978-82: 38% 1994-98: 42%
USA								
Chan et al. (110)	USA	1988-2001	Cohort SEER	30,246	No borderline	Disease specific Stratified on type	5 yr survival	5 yr survival: 1988-92: 45.4% 1993-97: 48.6%
Barnholtz-Sloan et al. (111)	USA	1973-2000	Cohort Population-based SEER	32,845	Epithelial No borderline Excluded: subjects lost to follow-up	Relative Stratified on age, race, marital status, surgery, stage, and type	2 and 5 yr sur-vival	5 yr rel. survival: 1973-79: 37% 1980-89: 39% 1990-97: 43%
Averette et al. (78)	USA	1985-1996	Cohort	17,114 1985-86: 8,603 1991: 8,919		Stratified on age	1-, 2-, 3-, 4-, 5-year survival	1985-86 and 1991: 5 yr survival: 41% <60 yr: 56% 60-69 yr: 34% 70-79 yr: 25% 80+: 21%
Australia								
Laurvick et al. (112)	Australia	1982-2000	Cohort Population-based	1,336 (1,126 surgery) (210 no sur-gery)		Relative Stratified on surgery (yes/no)	30 days, 1- 3- and 5-year survival	5 yr rel. survival: +surgery: 42.5% -surgery: 17.7% 1982-87: 38.8% 1988-93: 46.7% 1994-98: 53.5%

Table III. Studies of the impact of comorbidity in patients with ovarian cancer

(comorbidity: +/- co, HR: hazard ratio)

Authors	Country	Study period	Design	Type of comorbidity index used	Number	Adjustment	Risk estimates	Results
O'Malley et al. (95)	USA	1994-1996 (Follow-up 2001)	Cohort Population-based	Charlson (0,1+)	1,051 women (not borderline, epithelial, stage IC-IV, survived surgery for at least 12 days)	Stage, grade, histology, age, region of residence, chemotherapy	HR Unadjusted 5-yr survival Ovarian cancer death	HR_{adj}=1.4 5-yr survival: 21% (Charlson 1+) vs. 37% (Charlson 0)
Du Bois et al. (96)	Germany	Patients collected quarterly in 2001 Survival data up to 2 years	Cohort	Unspecified Dichotomy	476 women (34% of 1,413 diagnosed ovarian cancer patients, epithelial, not borderline)	Stage, age, PS (performance status), ascites, study participation, histology, grade, hospital volume)	HR overall All cause death	HR_{adj}=1.77
DiSilvestro et al. (98)	USA	1987-1992 4-year follow-up was available for 92% of the patients	Cohort Hospital-based	Modified Charlson (0,1+) and Kaplan and Feinstein	137 women (not borderline)	Stage, symptom stage, age	HR 3- and 4-yr survival All cause death	HR_{adj}=1.04 3-yr: 65% (- co) vs. 59% (+co) 4-yr: 60% (-co) vs. 55% (+co)
Maas et al. (99)	The Netherlands	1995-2001 (vital status up to Jan 1st 2004)	Cohort Population-based	Slightly modified Charlson Diseases present at the time of diagnosis	1,116 women (564 women FIGO stage II and III, epithelial, not borderline)	Age (<70 yrs/>= 70 yrs), FIGO stage II/III, treatment, period of diagnosis	HR 3 yr survival stratified on age (<70 yrs/>= 70 yrs) All cause death	HR_{adj}=1.2 (p=0.2) < 70 yrs: 54% (- co) vs. 50% (+ co) >= 70 yrs: 33% (- co) vs. 17% (+ co)
Janssen-Heijnen et al. (100)	The Netherlands	1995-2004 (vital status up to Jan 1st 2004)	Cohort Population-based	Slightly modified Charlson Diseases present at the time of diagnosis. No. of comorbid conditions	1,011 women	Age, stage, treatment	HR Details not given Relative survival as a measure of disease specific survival	No independent prognostic effect
Tingulstad et al. (28)	Norway	1987-1996 Follow-up 2001	Cohort Population-based	Charlson	571 women (not borderline)	Age, stage, grade, histology, residual tumour, treating hospital, CA 125, time period	HR Details not given All cause death	No independent prognostic effect in a multivariate analysis.
Piccirillo et al. (97)	USA	1995-2001	Cohort Hospital-based	ACE-27 (none, mild, moderate, severe)	Gynecological: 2,535 Of these 599 had ovarian cancer	Age, race, stage	HR (only for gynaecologic cancers not ovarian cancer specific) All cause death	HR_{adj}=1 (none, ref.) HR_{adj}=1.13 (mild) HR_{adj}=1.24 (moderate) HR_{adj}=2.04 (severe)

1.6 Conclusion

Ovarian cancer is a serious disease with poor survival. For unknown reasons, survival after ovarian cancer is poorer in Denmark than in other countries, however, the published data on survival after ovarian cancer among Danish women may not be up to date. In order to ensure quality of care for ovarian cancer patients, we need quality assurance systems. Administrative hospital data thus represent a potentially important source for monitoring ovarian cancer survival, primarily because the data are updated daily; however, little information exists on the quality of ovarian cancer-related data in the HDR.

Further, studies of prognostic factors are important to predict disease outcome, to define risk groups and to guide clinical decision-making. In the existing literature we found evidence of an association between the risk of ovarian cancer and having an episode of VTE prior to the cancer diagnosis. To our knowledge, no study has examined the specific prognosis of ovarian cancer patients with this complication.

Ovarian cancer incidence increases with age, as does the frequency of coexisting diseases. Comorbidity in ovarian cancer patients may be an important factor affecting patient care. Comorbidity can affect the timing of diagnosis, influence prognosis and choice of therapy and it can confound analysis. In the existing literature, we found few studies examining the impact of comorbidity on ovarian cancer survival; however, their findings were conflicting. None of the studies examined whether stage or age could explain the association.

The main conclusions are:

- In Denmark, survival of ovarian cancer is poor compared with other countries. This finding is discouraging yet the reported Danish findings are old, implying that the survival may have improved in the recent years.
- We need updated survival estimates and a system for the departments to continuously monitor the effectiveness of the clinical care of ovarian cancer patients.
- We need more knowledge regarding prognostic factors. VTE is a predictor of poor outcome in cancer patients generally, but concrete estimates are unknown for ovarian cancer.
- The evidence about the impact of comorbidity on prognosis among ovarian cancer patients is sparse and conflicting, and none of the existing studies was conducted in a

large group of ovarian cancer patients (all stages and histological types) in a population-based setting.

Properly designed epidemiological studies based on validated data sources are needed. In this thesis we conducted one validation study and four historical cohort studies using population-based registries, which, thanks to the unique civil registration number, enable the study of a large population of ovarian cancer patients with a complete follow-up.

2 Aims of the thesis

1) To evaluate the quality of data on ovarian cancer diagnoses in the regional Hospital Discharge Registry and to quantify the impact of any misclassification of discharge diagnoses on ovarian cancer survival (Study I).
2) To examine the survival of patients with ovarian cancer in Northern Denmark, from 1985 to 2004 (Study II).
3) To examine the impact of previous venous thromboembolism on the ovarian cancer survival (Study III).
4) To study the effect of comorbidity on the ovarian cancer survival (Study IV), taking tumour stage into consideration (study V).

3 Subjects and methods

3.1 Study-design

Study I

To evaluate the data quality of the ovarian cancer diagnosis in the regional HDR, we compared the registration of individuals from the regional HDR with registration of individuals in an independent reference source (DCR) (113).

A two by two table was constructed:

Data source 1 (regional HDR)	Data source 2 (DCR)		
	Registered ovarian cancer	Non-registered ovarian cancer	
Registered ovarian cancer	a	b	a+b
Non-registered ovarian cancer	c	d	c+d
	a+c	b+d	

We carried out case-by-case comparison. The concept of completeness is closely related to the concept of sensitivity (113), therefore the completeness was computed as:

completeness= a/(a+c).

Since the value of d (ovarian cancer not registered in any of the two registries) was not known, specificity could not be computed. However, the background population is big and the ovarian cancer is rather rare, therefore it is reasonable to assume perfect specificity (113).

The validity concept of the registration of cases is closely related to the concept of the predictive value of a positive registration (the ratio of the number of correctly registered ovarian cancers to all cases recorded in the registry that is being validated) (113). Positive predictive value (PPV) was computed as:

PPV= a/(a+b)

Studies II-IV

In these studies we employed the historical cohort design. The term *cohort* describes any designated group of persons whose experience is observed (followed) over a period of time (24). The main feature of the cohort study is observation of groups over a period, with subsequent comparison of incidence rates of disease or death in groups that differ in exposure levels (24). The cohort design in general can be time consuming and it can sometimes be impossible to assemble sufficiently large cohorts and to follow them prospectively for a time period that is sufficiently long to allow meaningful measurement. One way to overcome this problem is to use a historical cohort study, in which investigator reconstructs past exposures and outcomes form existing records (24). Danish registries are well known to offer such study opportunities.

3.2 Data sources

The first study of this thesis was conducted in North Jutland County, Denmark, within a population of approximately 500,000 inhabitants. Studies II and IV were conducted in Northern Denmark (North Jutland, Aarhus, Viborg and Ringkjobing counties), within a population of approximately 1.6 million inhabitants. The studies III and V were conducted nationwide, within a population of approximately 5.4 million inhabitants.

The entire population in Denmark has free access to tax-supported medical care, including hospitalisations. Hospital medical services are population-based, with practically no private inpatient ovarian cancer treatment. During the study period, treatment of ovarian cancer was not centralised in Denmark.

The five studies were based on data from the data sources described below.

The hospital discharge registry (HDR)

Since 1977, Danish counties have developed administrative information systems (regional hospital discharge registry) and used them routinely to monitor hospital admissions and discharges, waiting lists, operations, and treatment (in Viborg County since 1972). Data from these systems are transferred to the National Danish Hospital Discharge Registry. Data include civil registration number (the CPR number), dates of admission and discharge, the surgical procedure(s) performed, and up to 20 physician-assigned discharge diagnoses, which are classified according to the Danish version of the International Classification of Diseases (ICD), using the 8th revision until the end of 1993 and the 10th revision thereafter (114).

Aarhus University Hospital Research Database carries key information on all patients from the regional hospital discharge registries (HDRs) in four counties (North Jutland, Aarhus, Viborg and Ringkjobing).

The Danish Cancer Registry

The Danish Cancer Registry (DCR) is a population-based registry containing data on the incident cases of cancer throughout Denmark since 1943 (22). This registry stores administrative data (*e.g.* CPR number, county, and municipality), dates of diagnosis (month, year), the extent of tumour spread at the time of diagnosis, types of treatment, and diagnostic method. In 1987 notification by physicians of malignant and related diseases to the DCR became compulsory. Annual linkages to the HDR and the Danish Registry of Causes of Death ensure that missing reports are subsequently included. This process increases the completeness of the DCR but delays data availability. Furthermore, the specific departments are not able to obtain information (at department level) from the DCR in an easy way. All DCR data are reclassified to the modified ICD-7.

The County Pathology Registry

The Department of Pathology at Aalborg Hospital has computerised histopathology and cytology records for all histologically confirmed cases of cancer in the county. The records include the date of diagnosis and CPR number. In study I, pathology records on the patients identified in only one of the two registries (regional HDR or DCR) were reviewed, if these records were available. It was only possible to link data from the regional HDR or DCR to the County Pathology Registry as a manual search of individual electronic files.

The Civil Registration System

Since 1968, a unique 10-digit identifier (the CPR number) has been assigned to each Danish resident by the Central Office of Civil Registration, and we used this number to link data from the registries (115). The Civil Registration System contains information on vital status, date of death, and addresses of all Danish residents.

3.3 Definition on study population, exposure, and outcomes

Table IV. The structure of the studies II-V.

Study	Period of cancer diagnosis	Study population	Prognostic factors	Outcome and effect measure
II	1985-2003	Patients with incident ovarian cancer in North Jutland, Aarhus, Viborg, and Ringkjobing County	Age, Calendar time	1 and 5-year survival and MRR
III	1980-2003	Patients with incident ovarian cancer in Denmark	VTE	1 and 5-year survival and MRR
IV	1995-2004	Patients with incident ovarian cancer in North Jutland, Aarhus, Viborg, and Ringkjobing County	Comorbidity	1 and 5-year survival and MRR
IV	1995-2003	Patients with incident ovarian cancer in Denmark	Comorbidity	1 and 5-year survival and MRR

Ovarian cancer

Data on ovarian cancer in all five studies were obtained from the regional HDR and/or the DCR. We included all patients with a diagnosis of ovarian cancer. In study V, we restricted the study population to patients older than 15 years of age. We decided to exclude children since ovarian cancer in childhood is rare and often has a different clinical picture compared with adults.

The diagnosis of ovarian cancer was based on ICD-8 codes and ICD-10 codes in the regional HDR and on modified ICD-7 codes in DCR (Table V).

Table V. ICD-codes used to identify ovarian cancer patients in the regional Hospital Discharge Registry and the Danish Cancer Registry.

	The regional Hospital Discharge Registry		The Danish Cancer Registry
	ICD-8	ICD-10	ICD-7
Invasive ovarian cancer	183.00-03, 183.08-09	C56.0-C56.9	175.0, 175.1, 175.2, 175.3, 375.0, 475.0, 875.0
Borderline tumours			575.0-575.5

In study I, we compared patients registered in the regional HDR with patients registered in DCR. For validation we obtained information on the diagnosis from the County Pathology Registry on patients only registered in one of the two registries.
In studies II and IV, we used the regional HDR from North Jutland, Aarhus, Viborg, and Ringkjobing counties to identify ovarian cancer patients, who defined the study population. Studies III and V were based on nationwide data. We used the DCR to identify patients with invasive ovarian cancer thus excluding patients with borderline tumours.

Mortality

The outcome in the prognostic studies II-V was death. The main outcome measures were crude survival rates and cumulative all-cause mortality after 1 year and 5 years of follow-up after the date of ovarian cancer diagnosis. We did not attempt to determine the cause of death (e.g. the fraction of deaths attributable to ovarian cancer).

Prognostic factors (exposures)

Age and calendar time were used as prognostic factors in study II. In study III, the prognostic factor was VTE prior to the ovarian cancer diagnosis. Comorbidity was the prognostic factor in study IV and study V, using three categories (see below).

Venous thromboembolism

In study III a diagnosis of VTE before ovarian cancer diagnosis was the prognostic factor under study. We used HDR to identify episodes of VTE prior to the ovarian cancer diagnosis. Under this definition, we included lower-extremity deep venous thrombosis and pulmonary embolism. The codes used were 45099 and 45100 in ICD-8, and DI260, DI269, DI269A, DI801, DI802, DI802B, DI803, DI803D, DI803E, DI803F in ICD-10. We excluded episodes of

superficial thrombosis and upper-extremity deep venous thrombosis (because these often arise secondary to treatment). The date of admission to the hospital with a diagnosis of VTE was assigned as date of diagnosis of VTE. In order to exclude cases of VTE arising as complications of other diseases, only cases with VTE recorded as the primary diagnosis were included. We defined an unprovoked VTE as 1) unrelated to previous cancer, 2) unrelated to previous surgery, and 3) unrelated to pregnancy.

Comorbidity

In studies IV and V comorbidity was the potential prognostic factor, and in study III comorbidity was a potential confounder of the main association under study (Prior VTE and survival). We used the Charlson Comorbidity Index to classify comorbidity level (65), using data from the HDR. We computed the Charlson Comorbidity Index for all of the patients in study III-V using ICD-8 and ICD-10 codes (see Appendix). Within this index, malignant diseases are categorized in four groups: solid tumour, lymphoma, leukaemia, or distant metastasis. We excluded ovarian cancer when computing the index, because this diagnosis defined our study population. We classified the ovarian cancer patients into three groups according to the degree of comorbidity: i) patients with Charlson Comorbidity score 0, ii) patients with Charlson Comorbidity score 1-2, and iii) patients with Charlson Comorbidity score 3 or higher.

3.4 Definition of other variables

Stage

In the DCR we obtained information on stage of ovarian tumours. In this registry stage was classified either using the FIGO classification (see Table VI) or as local, regional spread, and distant metastasis (116). In study III, we reclassified the stages into FIGO-stages (FIGO I including local spread, FIGO II, FIGO III including regional spread, and FIGO IV including distant metastasis). Later, during the fifth study, we discovered that tumours categorized as regional spread included both FIGO-stage II and III tumours, therefore we categorized the ovarian cancer cases into four groups, as previously used by Kjaerby-Thygesen et al. (4): (a) localized tumours/FIGO-stage I tumours; (b) tumours with regional spread/FIGO-stage II and III tumours; (c) tumours with distant metastases/FIGO-stage IV tumours; and (d) tumours with unspecified stage (4).

Table VI. Ovarian cancer FIGO-stage classification

Table 1: Carcinoma of the ovary-Staging

FIGO		TNM
	Primary tumour cannot be assessed	TX
0	No evidence of primary tumour	T0
I	Tumour confined to ovaries	T1
IA	Tumour limited to one ovary, capsule intact No tumour on ovarian surface No malignant cells in the ascites or peritoneal washings	T1a
IB	Tumour limited to both ovaries, capsules intact No tumour on ovarian surface No malignant cells in the ascites or peritoneal washings	T1b
IC	Tumour limited to one or both ovaries, with any of the following: Capsule ruptured, tumour on ovarian surface, positive malignant cells in the ascites or positive peritoneal washings	T1c
II	Tumour involves one or both ovaries with pelvic extension	T2
IIA	Extension and/ or implants in uterus and/or tubes No malignant cells in the ascites or peritoneal washings	T2a
IIB	Extension to other pelvic organ No malignant cells in the ascites or peritoneal washings	T2b
IIC	IIA/B with positive malignant cells in the ascites or positive peritoneal washings	T2c
III	Tumour involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis and/or regional lymph nodes metastasis	T3 and/or N1
IIIA	Microscopic peritoneal metastasis beyond the pelvis	T3a
IIIB	Macroscopic peritoneal metastasis beyond the pelvis 2 cm or less in greatest dimension	T3b
IIIC	Peritoneal metastasis beyond pelvis more than 2cm in greatest dimension and/or regional lymph nodes metastasis	T3c and/or N1
IV	Distant metastasis beyond the peritoneal cavity	M1

Note: Liver capsule metastasis is T3/ Stage III, liver parenchymal metastasis M1/ Stage IV. Pleural effusion must have positive cytology.

From http://www.figo.org/docs/staging_booklet.pdf

Treatment

We retrieved information on treatment of ovarian cancer through the DCR. This registry contains information on treatment of the cancer within the first four months after the diagnosis. An indicator variable (yes/no) is assigned for each treatment type – surgery, chemotherapy, radiation, hormonal treatment, others – thus allowing for coding of any combination of these treatments (116). In this thesis we categorized the treatment variables in to five groups: combined surgery and chemotherapy, surgery only, chemotherapy only, other treatment, and symptomatic or no treatment.

3.5 Statistical analyses

In **study I**, we estimated the completeness of registration of ovarian cancer patients in regional HDR by calculating the proportion of patients registered with ovarian cancer in the DCR who also had ovarian cancer diagnosis in the regional HDR. The numerator was the number of patients registered in both registries and the denominator was the number of all the patients registered in the DCR (113). We defined PPV (positive predictive value) as the proportion of patients registered with ovarian cancer in the regional HDR who also had an ovarian cancer diagnosis in the DCR (113). The numerator was the number of patients registered in both registries and the denominator was the number of all patients registered in the regional HDR. We analysed data with and without including borderline tumours in the data from the DCR. To compare survival estimates for patients registered in the regional HDR with survival estimates for patients registered in the DCR, we constructed Kaplan-Meier survival curves for each of the two data sources and used Cox's proportional hazards regression to estimate the mortality rate ratios (MRR) and associated 95% confidence intervals (CI).

In **study II**, we constructed Kaplan-Meier survival curves counting the survival time from the date of ovarian cancer diagnosis; these were stratified into four five-year calendar periods. We estimated the one- and five-year survival rates within three age strata. We computed the MRRs for the four five-year calendar periods, treating the period from 1985 to 1989 as the reference. The age-adjusted one- and five-year MRRs were estimated with the same reference period. All patients were followed until death, emigration, or January 31, 2005.

In **study III**, the prevalence of patients with ovarian cancer and VTE who had FIGO stage IV disease was compared with the prevalence of all other ovarian cancer patients who had FIGO stage IV disease by computing the prevalence ratio, adjusted for age using Mantel-Haenszel method.
We summarized the survival of ovarian cancer patients using Kaplan-Meier survival curves. The proportions of patients surviving at one year with and without VTE were computed. We used Cox's proportional hazards regression to compare the mortality among the cancer patients with and without VTE. The MRR was computed separately, for one year and from one year and the rest of the follow-up period post-diagnosis. We adjusted the analysis for age, year of diagnosis, comorbidity, and FIGO stage. Patients were followed from the date of the ovarian cancer diagnosis until death or the end of the follow-up period (December 31, 2005), whichever came sooner.

In **study IV**, we computed the occurrence of the 19 discrete medical conditions defined in the Charlson Comorbidity Index, which had been recorded in the ten years preceding the ovarian cancer diagnosis. We then computed the prevalence of comorbidity among study patients diagnosed during each calendar period. For each comorbidity level, we computed Kaplan-Meier survival curves by period of diagnosis and estimated survival at one and five years using the Kaplan-Meier product-limit method (24). Follow-up started on the date of ovarian cancer diagnosis and continued until death, emigration, or 31 January 2005. We used Cox's proportional hazards regression to compare mortality of ovarian cancer patients according to the level of comorbidity. For each of the three-year calendar periods, we computed one- and five-year age-adjusted hazard ratios as estimates of relative mortality. Patients with no comorbidity served as the reference group.

In **study V**, we compared the prevalence of patients with comorbidity who had distant metastases/FIGO IV with the prevalence of patients without comorbidity who had distant metastases/FIGO IV by computing the prevalence ratio, adjusted for age (using the Mantel-Haenszel method).
For each stage of ovarian cancer we computed Kaplan-Meier survival curves according to comorbidity group. To compare the mortality between cancer patients with and without comorbidity we used Cox's proportional hazards regression to compute one- and five-year crude and adjusted hazard ratios as a measure of MRRs (117). We used patients with no registered comorbidity as the reference group. First we adjusted for age and calendar time; thereafter we also adjusted for stage (four categories). We then defined design variables for the 12 combinations of stage and comorbidity. For each stratum of comorbidity and stage, we computed one- and five-year survival using the Kaplan-Meier product-limit method (24). We used Cox's proportional hazards regression to compare the mortality using patients with localized tumours/FIGO-stage I tumours and no registered comorbidity as the reference group and adjusting for age and year of diagnosis (3-year calendar periods). Additionally, we repeated the analyses while additionally adjusting for treatment. Finally, we repeated the analyses in a subgroup of ovarian cancer patients who had received either surgery, chemotherapy or both.

We assessed the assumption of proportional hazards in the Cox's model graphically. All estimates were obtained with corresponding 95% confidence intervals (95% CI). Analyses were

performed using: SAS® System, 8.2 (study I); SAS version 9.1.3 (SAS Institute Inc., Cary, NC, USA) (study II, III and IV); and STATA version 9.2 (study V).

The project was approved by The Danish Data Protection Agency (2004-41-4353).

4 Results

Below follows a summary of the main results obtained in the five studies.

4.1 Study I

We identified 489 patients registered with a first-time ovarian cancer diagnosis in either the regional HDR or the DCR, in 1994–1999. Of these, 411 (84%) were found in both registries (including borderline tumours in the DCR), 59 (12%) were found only in the regional HDR and 19 (4%) were found only in the DCR. Eighty-seven (18%) of the patients with ovarian cancer diagnosis in the regional HDR actually had borderline tumours.

Completeness and positive predictive value (PPV)

Using the DCR (including borderline tumours) as the reference standard, the completeness of ovarian cancer cases in the regional HDR was 96% (95%CI: 94%–98%) and PPV was 87% (95%CI: 85%–90%).

When borderline tumours were excluded from the DCR data, the PPV declined to 69% and the completeness did not change (see Table VII). Completeness did not substantially vary by age group, while the PPV tended to decline with age (see Table VII).

Table VII. Number of patients with a first-time diagnosis of ovarian cancer. Degree of completeness and positive predictive value (PPV) are given as percent

	Patients registered in:			Total	Degree of completeness	Positive predictive value
	Both registries	Only HDR	Only DCR			
	n (%)	n (%)	n (%)	n	% (95% CI)	% (95% CI)
DCR borderline tumours excluded	324 (67)	146 (30)	15 (3.1)	485	96 (93-97)	69 (65-73)
DCR borderline tumours included	411 (84)	59 (12)	19 (3.9)	489	96 (94-98)	87 (85-90)
DCR borderline tumours included						
< 50 year	97 (87)	7 (6.3)	7 (6.3)	111	93 (89-98)	93 (89-98)
50-75 year	247 (86)	35 (12)	6 (2.0)	288	99 (96-99.5)	88 (84-91)
> 75 year	65 (71)	19 (21)	8 (8.7)	92	89 (82-96)	77 (68-86)

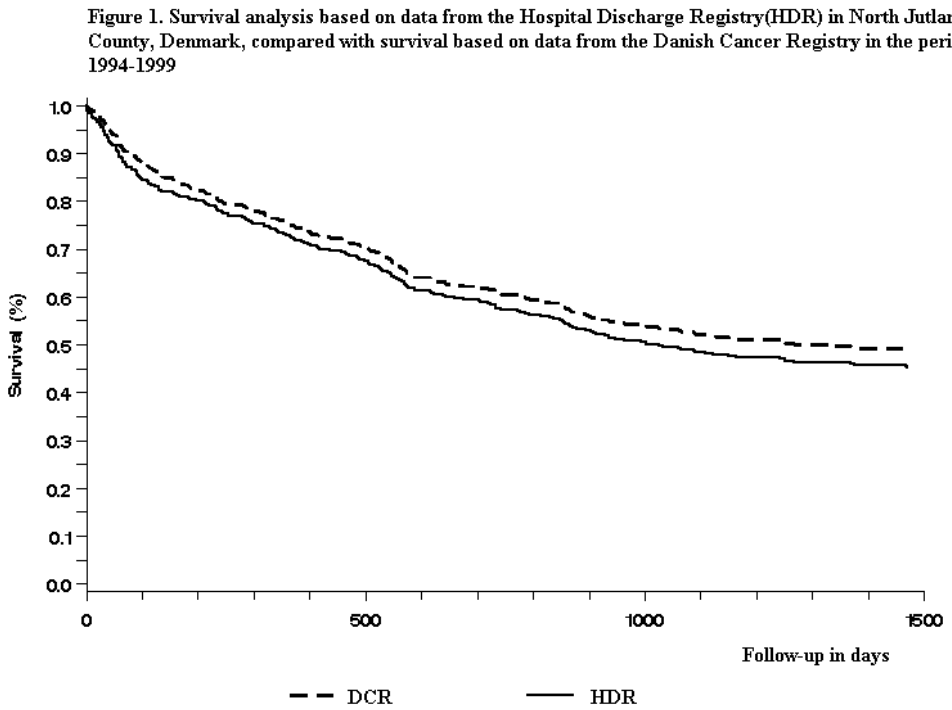
Validity of the diagnosis

We reviewed histological diagnoses for all patients (with borderline tumours included in the DCR) identified in only one of the registries by manually searching individual electronic files in the County Pathology Registry. For the 19 patients registered only in the DCR, the diagnosis was judged as correct or most likely correct in 14 (74%) of the cases. For the 59 patients registered only in the regional HDR, the diagnosis was judged as correct or most likely correct in 32 (54%) of the cases. Of the 470 patients registered with an ovarian cancer diagnosis in the regional HDR, 26 (5.5% [95% CI: 3.5%–7.6%]) patients could not be confirmed as having this diagnosis either by registry in the DCR or by pathological review. In the DCR (borderline tumours included) the false-positive rate was 1.2% (5/430).

Survival

Survival curves obtained for ovarian cancer patients based on diagnoses (including borderline tumours) registered in the regional HDR and in the DCR are shown in Figure 3. The curves show slightly higher mortality rates for patients registered in the regional HDR. Accordingly, the MRR from the proportional hazards regression comparing the regional HDR-based patients' survival with the DCR-based patients' survival was 1.08 (95%CI: 0.90-1.29).

Figure 3. Survival analysis based on data from the regional HDR and DCR, 1994-1999



4.2 Study II

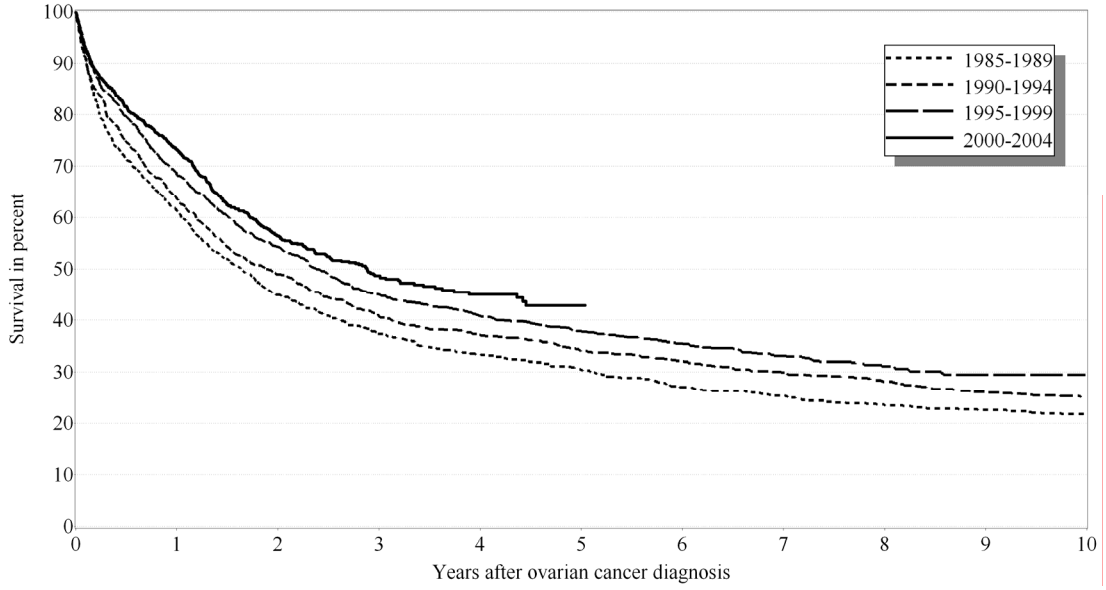
We identified 3,719 patients diagnosed with ovarian cancer for the first time from 1985 to 2004. The age distribution of ovarian cancer patients over the study period varied little (median age was consistently about 63 years).

Survival

The overall survival curves according to four calendar periods showed improved survival over the years (Figure 4). Compared with patients diagnosed during 1985-1989, those diagnosed during 2000-2004 had about 10 percent lower mortality rates.

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

Figure 4. Survival of ovarian cancer in four time periods



Age-specific survival

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

The five-year survival also improved between 1985-1989 and 1995-1999. The increase was most pronounced among patients 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% (see Table VIII).

Mortality

The age-adjusted one-year MRR was 0.65 in 2000-2004 compared with 1985-1989; and the age-adjusted five-year MRR was 0.80 in 1995-1999, with 1985-1989 as reference period.

Table VIII. One- and five-year absolute survival (95% CI) among ovarian cancer patients in three different age groups, according to calendar period of diagnosis

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

4.3 Study III

Of 12,835 ovarian cancer patients, 128 were registered with an ovarian cancer diagnosis subsequent to a diagnosis of VTE. Fifty patients were diagnosed with ovarian cancer within 4 months after the VTE, and 78 were diagnosed more than 4 months after the VTE diagnosis.

FIGO stage and VTE

Compared with ovarian cancer patients without VTE, the distribution of tumour stage was slightly shifted toward later stages among patients with VTE. When ovarian cancer patients with FIGO stage IV diagnosed within four months after VTE were compared with VTE-free ovarian cancer patients who had FIGO stage IV, age-adjusted prevalence ratio was 1.1 (95% CI, 0.8–1.5). Among the patients in whom ovarian cancer was diagnosed more than four months after the VTE, age-adjusted prevalence ratio was 1.1 (95% CI=0.8–1.5).

Survival

Figure 5 shows unadjusted survival curves for patients in whom ovarian cancer was diagnosed within four months after VTE and for ovarian cancer patients without VTE. Patients in whom ovarian cancer was diagnosed more than four months after the episode of VTE also had a poor prognosis. One-year survival was 44% (95% CI, 33–60%) for patients with ovarian cancer diagnosed within four months after VTE and 54% (95% CI, 44–66%) for patients with ovarian cancer diagnosed more than four months after VTE, compared with the one-year survival of 63% (95% CI, 62–64 %) among patients without VTE. The respective MRRs adjusted for age, calendar time, comorbidity, and FIGO-stage were 1.7 (95% CI, 1.2–2.5) and 1.2 (95% CI, 0.8–1.7) (see Table IX).

Figure 5. Unadjusted Kaplan-Meier survival comparing patients with ovarian cancer diagnosed within four months after an episode of VTE with VTE-free ovarian cancer patients

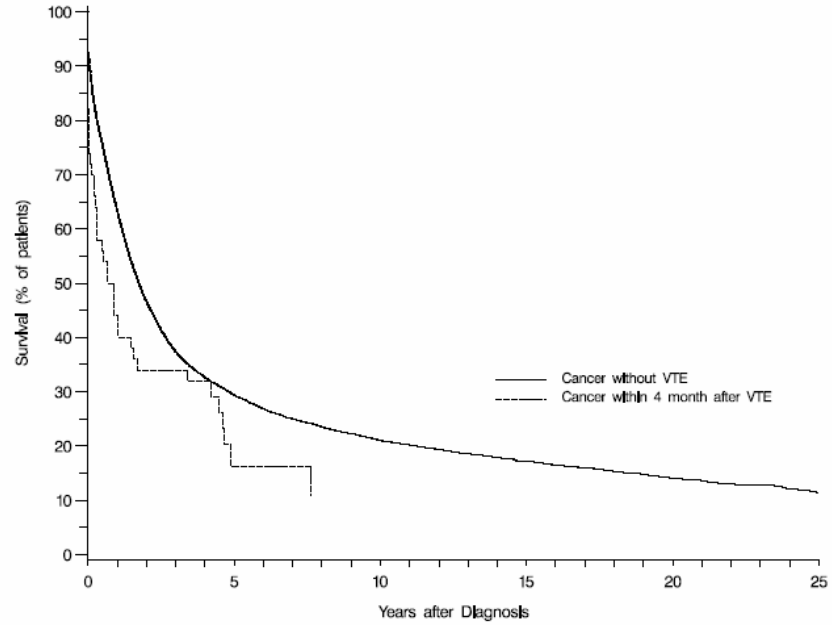


Table IX: One-year survival and mortality ratios during the first year of follow-up

	One year survival	Unadjusted mortality ratio	Adjusted mortality ratio [a]
Ovarian cancer without VTE (control group)	63% (62–64%)		
Ovarian cancer within 4 months after VTE	44% (33-60%)	1.8 (1.3-2.7)	1.7 (1.2-2.5)
Ovarian cancer 4 months to 27 years after VTE	54% (44-66%)	1.4 (1.0–1.9)	1.2 (0.8–1.7)

[a] Adjusted for age, calendar-time, comorbidity and FIGO-stage.
Associated 95% confidence interval (CI) is shown in the parenthesis.

4.4 Study IV

There were 1,995 patients with a first-time ovarian cancer diagnosis between 1995 and 2004. Approximately one-third of them received unspecific diagnosis of ovarian cancer, whereas the rest had stage specified in the diagnosis.

Prevalence of comorbidity

No comorbidity was recorded for 1,525 (76%) ovarian cancer patients; 379 (19%) had Charlson score 1-2, and 91 (5%) had Charlson score 3+. The proportion of patients without registered comorbidity decreased from 81% to 75% during the study period. At the same time, the proportion of patients with Charlson score 1-2 increased from 16% during the 1995-1999 period to 21% during the 2000-2004 period, and the prevalence of patients with Charlson score 3+ remained essentially unchanged (4%-5%).

Survival

One-year overall survival increased from 68% (95% CI, 64%-71%) in 1995-1997 to 73% (95% CI, 70%-76%) in 2001-2004. Overall five-year survival did not change appreciably over time.

For patients without comorbidity a better survival was observed among patients diagnosed in 2001-2004 than among patients diagnosed in 1995-1997 and 1998-2000. Survival curves in patients with Charlson score 1-2 and 3+ showed no improvement during the study period. In Table X, we present one- and five-year survival estimates corresponding to the survival curves.

For patients with Charlson score 1-2, the one-year age-adjusted MRR was 1.1 (95% CI, 0.8-1.6) for those diagnosed with ovarian cancer in 1995-1997, 1.3 (95% CI, 1.0-1.8) for those diagnosed in 1998-2000, and 1.7 (95% CI, 1.3-2.4) for those diagnosed in 2001-2004 (see Table X), all compared with patients with Charlson score 0. Higher MRRs were observed in patients with Charlson score 3+. The one-year age-adjusted MRR was 2.4 (95% CI, 1.4-4.3) for those diagnosed with ovarian cancer in 1995-1997, 1.6 (95% CI, 1.0-2.7) for those diagnosed in 1998-2000, and 2.2 (95% CI, 1.3-3.8) for those diagnosed in 2001-2004 (see Table X).

The five-year age-adjusted MRR for patients with Charlson score 1-2 was 1.1 (95% CI, 0.8-1.4) for those diagnosed with ovarian cancer in 1995-1997 and 1.1 (95% CI, 0.8-1.3) for those diagnosed in 1998-2000 (see Table X). Among patients with Charlson score 3+, the age-adjusted five-year MRRs were 1.7 (95% CI, 1.0-2.7) for those diagnosed in 1995-1997 and 1.6 (95% CI, 1.1-2.3) for those diagnosed in 1998-2000 (see Table X).

Table X. One- and five-year survival and the crude and age-adjusted one- and five-year all-cause mortality rate ratios (MRR) by comorbidity levels in the three time periods. The corresponding 95% confidence intervals are given in parentheses

Year of diagnosis		Charlson score		
		0	1-2	3+
1995-1997				
	Number	517	101	24
	Median age, years	61	72	67
One year				
	Survival	71% (67%-75%)	58% (48%-67%)	46% (26%-64%)
	Age adj. MRR	1 (ref.)	1.1 (0.8-1.6)	2.4 (1.4-4.3)
Five years				
	Survival	41% (36%-45%)	28% (19%-37%)	29% (13%-48%)
	Age adj. MRR	1 (ref.)	1.1 (0.8-1.4)	1.7 (1.0-2.7)
1998-2000				
	Number	492	135	34
	Median age, years	61	70	73
One year				
	Survival	75% (71%-79%)	59% (50%-67%)	50% (32%-65%)
	Age adj. MRR	1 (ref.)	1.3 (1.0-1.8)	1.6 (1.0-2.7)
Five years				
	Survival	43% (38%-47%)	30% (22%-38%)	18% (7%-32%)
	Age adj. MRR	1 (ref.)	1.1 (0.8-1.3)	1.6 (1.1-2.3)
2001-2004				
	Number	516	143	33
	Median age, years	59	72	68
One year				
	Survival	79% (75%-82%)	58% (49%-66%)	52% (34%-67%)
	Age adj. MRR	1 (ref.)	1.7 (1.3-2.4)	2.2 (1.3-3.8)

- It was not possible to compute a five-year survival or mortality for the period 2001-2004, because of the relatively short follow-up period.

4.5 Study V

We identified 5,213 patients above 15 years of age with ovarian cancer diagnosed from 1995 to 2003. Of those patients, 3,727 (72%) had no comorbidity recorded in the HDR, 1,116 (21%) had comorbidity score 1-2, and 370 (7%) had comorbidity score 3+.

Information on stage was found for 94% of the ovarian cancer patients in DCR, which was in contrast to patients identified in the regional HDR (study IV), where only 66% had information on stage. An association between comorbidity and advanced stage was found only among patients with severe comorbidity. Among patients with severe comorbidity, 42% had distant metastases/FIGO IV, compared to 28% of patients without comorbidity (age-adjusted prevalence ratio=1.3, 95% CI, 1.1–1.5).

Comorbidity and mortality

In table XI the estimates of one- and five-year MRRs for the three levels of comorbidity are shown. After adjustment for age and calendar time, the one-year MRRs declined from 1.8 to 1.4 and from 2.7 to 2.0 (for Charlson Comorbidity score 1-2 and 3+, respectively). The MRRs further declined to 1.3 and 1.8, respectively, when we included stage in the model.

Table XI. One- and five-year mortality rate ratio (MRR) in the three levels of co-morbidity

	Charlson Comorbidity score		
	0	**1-2**	**3+**
N (%)	3,727 (72%)	1,116 (21%)	370 (7%)
1-year follow-up			
MRR	1 (ref.)	1.8 (1.6-2.0)	2.7 (2.3-3.1)
Adj. MRR*	1 (ref.)	1.4 (1.2-1.5)	2.0 (1.7-2.3)
Adj. MRR**	1 (ref.)	1.3 (1.2-1.5)	1.8 (1.6-2.1)
5-year follow-up			
MRR	1 (ref.)	1.5 (1.4-1.6)	2.3 (2.1-2.6)
Adj. MRR*	1 (ref.)	1.3 (1.2-1.4)	1.8 (1.6-2.1)
Adj. MRR**	1 (ref.)	1.2 (1.1-1.4)	1.7 (1.5-1.9)

*Adjusted for age and calendar time. **Adjusted for age, calendar time and stage. The corresponding 95% confidence interval is given in parentheses.

Comorbidity, stage of cancer and survival

For all tumour stages, the survival curves showed a higher survival in patients without co-morbidity than in patients with registered comorbidity. The one- and five-year survival estimates are shown in Table XII.

The effect of severe comorbidity (3+) on ovarian cancer one-year mortality varied according to stage. Tumours with regional spread/FIGO stage II and III were associated with increased impact of severe comorbidity on mortality (Table XII). The impact of comorbidity score 1-2 on one-year mortality varied only slightly by stage. The variation in the effect of comorbidity on ovarian cancer five-year mortality by stage of cancer was similar to that for one-year mortality, although not as pronounced.

Accounting for treatment in the analysis did not remove the association between severe co-morbidity and mortality (data not shown) except for tumours with distant metastases/FIGO-stage IV, where the association disappeared.

Table XII. One-year survival and the one-year mortality rate ratio (MRR) in the three levels of comorbidity according to the stage of cancer

	Charlson Comorbidity score		
	0	1-2	3+
Localized tumour/FIGO-stage I			
Number	774	184	37
Median age, years	56	67	72
Survival in %	95 (93-97)	88 (82-92)	81 (64-91)
Adj. MRR	1 (ref.)	2.1 (1.2-3.5)	2.7 (1.2-6.2)
Regional spread/FIGO-stage II, III			
Number	1,757	492	157
Median age, years	62	68	69
Survival in %	77 (75-79)	63 (59-67)	47 (39-54)
Adj. MRR	4.8 (3.5-6.8)	7.1 (5.0-10.1)	12.3 (8.3-18.1)
Distant metastases/FIGO-stage IV			
Number	1,002	338	140
Median age, years	66	71	71
Survival in %	50 (47-53)	38 (33-44)	34 (27-42)
Adj. MRR	11.6 (8.3-16.2)	13.9 (9.8-19.8)	15.7 (10.7-23.1)
Unspecified			
Number	194	102	36
Median age, years	66	75	71
Survival in %	62 (55-68)	40 (31-50)	33 (19-49)
Adj. MRR	8.1 (5.5-12.1)	11.2 (7.4-16.8)	15.3 (9.1-25.7)

Adjusted for age and calendar time. The corresponding 95% confidence interval is given in parentheses.

5 Methodological considerations of the studies

As in all observational studies, we need to critically evaluate potential alternatives to a causal association before interpreting the findings as evidence of causality (118). We therefore have to consider systematic error, represented by bias in selection, information (measurement), and confounding, as well as random error, manifested in statistical imprecision. In this section we discuss these errors in relation to our studies.

5.1 Study I

We compared the ovarian cancer diagnoses in two registries using one of the registries (DCR) as the gold standard. The PPV of an ovarian cancer diagnosis in the regional HDR was better, when we included borderline tumours in data from the DCR, while completeness remained approximately the same. It is worth emphasizing that some of the tumours registered in the regional HDR as ovarian cancer are in fact borderline tumours, and thus a potential source of bias stemming from the regional HDR data. In the period up to April 1st 2007 it was not possible to separate borderline tumours from invasive ovarian cancer in HDR (119). But if sensitivity and PPV are stable over time, we do not expect this misclassification to bias relative survival estimates. We found that the misclassification had only a small impact on survival estimates.

Thus, the regional HDR is a useful data source in monitoring ovarian cancer survival in Denmark. Ovarian cancer data from the regional HDR appear to be suitable for research, although absolute survival estimates have to be interpreted with caution.
Our finding of the high quality of the ovarian cancer diagnosis may be valuable for evaluating strengths and weaknesses in studies II-V.

5.2 Studies II-V

5.2.1 Selection bias

Selection bias would arise in our studies if the association between a prognostic factor and mortality differs for those included into and excluded from the study cohorts (24), or if the association differs according to the length of available follow-up. In Danish registries, loss to follow-up is practically absent because of the highly efficient Civil Registration System (115); we therefore expect no selection bias due to loss of follow-up.

Since we used different source populations in different studies of this thesis (see Table IV); we will discuss separately potential sources of selection bias in studies II-V.
In **studies II and IV**, we included all patients with an ovarian cancer diagnosis in the regional HDRs from North Jutland, Aarhus, Viborg and Ringkjøbing counties. As shown in study I, we have included patients with borderline tumours. Up to 15% of ovarian cancer patients have borderline tumours (32), and since the prognosis of these patients (120) is far better than that for patients with invasive disease (overall five-year disease-related survival 86%), the absolute survival will be overestimated (**study II and IV**). However, we do not expect that relative estimates (MRR) be biased.

In **study IV**, the inclusion of patients with borderline ovarian tumours could impact the association between the presence of comorbidity and mortality following ovarian cancer diagnosis. Patients with borderline tumours are often younger and may be less affected by comorbidity than patients with invasive cancer. Thus, mortality among ovarian cancer patients without registered comorbidity could be underestimated. Although age was taken into consideration in the analysis, we cannot rule out the possibility that inclusion of borderline tumours produced exaggerated relative estimates.

The population of **study III** consisted of all ovarian cancer patients identified in the DCR, which is more than 95% complete (22). While using this registry we were able to exclude patients with borderline tumours. Patients were included in the study at the time of ovarian cancer diagnosis. Clinicians caring for patients with VTE could become more alert for cancer in these patients because of the known association of VTE with cancer. This could potentially result in earlier diagnosis of ovarian cancer in patients with VTE than in patients without VTE. This would bias the relative survival estimates towards the null. However, we found that advanced stage was associated with prior VTE; therefore we find that surveillance bias is unlikely to be a major problem in our study.

In **study V**, the study population was identified in the DCR and restricted to adult patients. Selection bias could occur if the indication for diagnosing ovarian cancer differed according to the presence of comorbidity (**study IV and V**). Patients with comorbidities are probably seeking medical care more often than patients without comorbidity; therefore it is possible that clinicians caring for patients with comorbid diseases were more likely to detect ovarian cancer in these patients than in patients without comorbid diseases. This could result in an underestimation of the MRR. On the other hand, since we found that advanced stage was

associated with comorbidity, indicating later detection of ovarian cancer in patients with co-morbidities, we may have overestimated the MRR.

5.2.2 Information bias

If information collected about our study participants is erroneous, a systematic error can arise (24). Such errors can result from misclassification of the exposure or the mortality. The misclassification can be either differential or non-differential, depending on its distribution among the comparison groups. For all studies the outcome was all cause mortality, in which we do not expect any misclassification.

In **study II**, age and calendar time were the prognostic factors under study. We categorized age into three groups (< 40 years, 40-59 years and 60 years or more). In the youngest group we had few patients compared with the oldest group, which was the largest. Such grouping may be too crude and could therefore lead to information bias and underestimation of MRR. The calendar time was categorized in groups of 5 years' duration; although sufficient, this categorization may as well have caused information bias.

In **study III**, information bias may have occurred as a result of misclassification of the prognostic variable (VTE). The diagnosis of VTE can be difficult (121;122), with clinical signs and symptoms not being sufficiently specific to establish or rule out the diagnosis. The diagnosis of VTE from the Swedish HDR is known to be misclassified in 10 to 20% of the cases (123), and a similar rate could be expected in the Danish HDR. Further, an American study indicated that 92% of the coded cases of PE were correct, and 79-84% of the cases of deep venous thrombosis were coded correct (124). This lack of specificity may lead to an underestimated difference in survival between the patients with VTE and those without it.

In **study IV and V**, comorbidity was the prognostic factor, and information bias may have occurred if there were misclassifications of the comorbid diseases in the HDR. In a study from Canada comprising 14,980 patients, the Charlson Comorbidity score has been shown to have a high specificity, but a variable sensitivity when compared with diagnoses abstracted from the medical charts (72). It is thus possible that some patients with comorbid conditions were classified erroneously as having no comorbidity, or some patients may have erroneously been classified as having moderate comorbidity (Charlson score 1-2) instead of severe comorbidity (Charlson score 3+). With the three comorbidity groups, misclassification of estimates could occur both toward or away from the null (125). The registration of comorbid

conditions may have become more complete over time, so any misclassification would have been greater in earlier periods. This could partially explain the improvement in survival among those with no comorbidity.

5.2.3 Confounding

In the studies we were able to adjust the analysis for age, calendar time, stage (study III, stratified in study V), comorbidity (study III), and treatment (study V). However, residual confounding, unmeasured confounding or unknown confounding could still affect our relative estimates. Residual confounding stems from incomplete control of measured confounding factors (24). Residual confounding stems from insufficiently detailed information, improper categorisation, and misclassification of one or more confounding variables. Unmeasured confounders are known possible confounding factors that could not be measured in the study. Unknown confounding is confounding by factors outside current knowledge.

The quality of the stage and treatment data in the DCR may be questionable. The stage of cancer at the time of diagnosis is based on a combination of pathologic, operative, and clinical assessments available within a short time of diagnosis (76). Information on stage was available in 94% of the ovarian cancer patients in the DCR, whereas it was only the case for 66% of the patients in the regional HDR. Misclassification of the stage may produce residual confounding. If the misclassification of stage was non-differential (i.e. unrelated to the presence of VTE or comorbidity (study III and V)), it would tend to cause overestimation of positive associations. Even though we categorized stage slightly differently in studies III and V, the MRRs changed little after adjustment for stage, speaking against substantial residual confounding by this factor.

The DCR provides information on the treatment within the first four months in a series of dichotomous variables. Misclassification of patients with respect to the treatment data on ovarian cancer could lead to residual confounding by treatment. Such misclassification has been described for breast cancer patients, where surgery was correctly coded in 95.4% whereas chemotherapy was correctly coded in 72.3% in the DCR (126). In a preliminary study, we reviewed 80 discharge abstracts from patients coded in the DCR as not having surgery. We found that 33% (26/80) of them actually had surgery for ovarian cancer. During our study period (1995-2003) treatment recommendations remained essentially the same. Therefore, misclassification of treatment is not expected to change over time. Still, only

treatment given within the first four months of diagnosis was reported and therefore the data may not reflect changes in treatment plans made due to complications of comorbidity. This misclassification would be differential, with unpredictable direction of bias.

The treatment data in the Danish Cancer Registry do not contain details on the aggressiveness of the surgery (only whether the operation was radical or not), type of chemotherapy or on any modification of chemotherapy. We used a crude categorization of the treatment variables, which could lead to residual confounding. But when we adjusted for treatment in study V, the MRRs only changed little, speaking against substantial residual confounding.

5.2.4 Precision

In this thesis we used 95% confidence intervals to report precision of our estimates; a method which is widely used in the international literature (24).

6 Discussion in relation to the existing literature

6.1 Study I

Accuracy of ovarian cancer ICD-10 diagnosis in a Danish population-based hospital discharge registry

To the best of our knowledge, this is the first study that validated ovarian cancer ICD-10 diagnosis in the regional Danish Hospital Discharge Registry. Only few Danish studies exist in which gynaecological ICD-8 discharge diagnoses have been validated. One of them assessed the validity of ICD-8 coding of non-malignant gynaecological conditions and found a PPV of 78% for benign ovarian tumours (127). The data quality of the regional HDR found in our study was slightly better than the data quality (ICD-8) reported by Kjaergaard at al. in another Danish study (128). We identified all ovarian cancer patients, whereas Kjaergaard at al. (128) restricted the study population to patients with operation codes indicating malignant gynaecological diseases and validated this against the registration of surgically treated gynaecological cancer in the Danish Cancer Registry. They found for ovarian cancer a completeness of 83% and a PPV of 90% (128). Our data suggest that use of a simpler and a more coherent classification of diseases (ICD-10) improves the validity in comparison with the highly detailed coding (ICD-8).

Little other data exist on the quality of ovarian cancer diagnosis in similar registries. In a Norwegian study investigators identified 945 patients with ovarian cancer recorded either in the hospital discharge registry or in the Norwegian cancer registry and demonstrated a nearly 100% completeness of the Norwegian Cancer Registry when borderline tumours were excluded (129). Yet not all registries have high quality of data. Using a Regional Cancer Registry, a British study found, among 829 cases of ovarian neoplasms (333 malignant or borderline, 496 benign), that only 611 (74%) were registered in the hospital admissions records (1979-1983) (130). Another British study, which included 49 ovarian cancer patients identified in a screening program of 22,000 women, showed that 22% of the ovarian cancer cases were missing from the cancer registry (131).

In our study, we chose to use the DCR as the reference standard. DCR, however, also contained misclassified cases. We estimated the under-notification of cases to be 1.2%, which would lead to an underestimate of the completeness and of the PPV from the regional HDR. Other Danish studies have found a deficit of 2.2% for cervical cancer (132) and of 0% for breast cancer (126).

In conclusion, the data quality of ovarian cancer diagnosis in the Danish regional HDR is high, and data are suitable for monitoring ovarian cancer survival.

6.2 Study II

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

Our findings are in agreement with a previous study based on data from the DCR. This study (19,476 patients) reported improved five-year survival over the period 1943 to 1987 (22.3% vs. 30.4%) (85). Another Danish study, conducted in a single county (Funen) and based on data from the HDR, included 412 patients with ovarian cancer, none of whom had borderline tumours (86). In contrast to our findings, the investigators found no improvement in five-year survival from 1973-1978 to 1981-1986 (86); even though we have included borderline tumours, that study yielded a five-year survival estimate that was slightly lower than ours for the period 1981-1986 (26.7%).

Several earlier European studies have likewise shown improved survival of ovarian cancer patients since the mid-1970s (42;89;90;103-106;109). Improved survival was also seen in the USA (110;111) and in Australia (112). At the same time, all other countries have consistently reported higher survival rates than that found in our study, despite the fact that several of them studies excluded borderline tumours (42;90;106;110;111). Two studies in Germany used period analysis, potentially explaining better survival estimates. We have identified ovarian cancer patients in the regional HDR, meaning that cases identified through autopsy or death certificate alone were not included; this could therefore not explain the finding of poor survival.

6.3 Study III

Prognosis of ovarian cancer subsequent to venous thromboembolism: A nationwide Danish cohort study

This study is one of the first ones that examined the prognosis of ovarian cancer patients with a preceding VTE diagnosis. Our findings agree with the findings by Sorensen et al. that cancer diagnosed at the same time as or within one year after an episode of VTE is associated with an advanced stage of tumour and a poor prognosis (93).

Studies in mice have indicated that the coagulation mechanism has a role in cancer development (133;134). This is supported by studies that show that the use of low-molecular-weight-heparin (LMWH) therapy in cancer patients may improve survival (135-137). However, this finding was not confirmed in another study in patients with advanced malignancy

treated with dalteparin (5,000 IU), a low molecular weight heparin preparation (138). As our study lacked information about antithrombotic treatment, we could not examine the impact of the type of antithrombotic treatment on mortality among ovarian cancer patients.
Still, our data, in combination with the studies of antithrombotics, provide an impetus for further studies of antithrombotic treatment of ovarian cancer patients.

6.4 Studies IV and V

Comorbidity and ovarian cancer survival in Denmark, 1995-2005: a population-based cohort study, and

The impact of comorbidity and stage on ovarian cancer mortality: a nationwide Danish cohort study

In study IV, using data from the regional HDR to identify ovarian cancer patients, we found that severe comorbidity was a predictor of a poorer survival. No comorbidity was recorded for 76% of the ovarian cancer patients, compared with 66% in a Norwegian study that likewise used the Charlson Comorbidity index (28). Compared with the Norwegian study, we found a lower prevalence of patients with an index score of 1-2 (19% vs. 32%), and a higher prevalence of patients with an index score of 3 or more (5% vs. 2%) (28). A study in the US and a study in the Netherlands, which used different methods for collecting data on comorbidity, found lower proportions of ovarian cancer patients without comorbidities than we did (51% and 49%, respectively) (62;99). The American study reviewed medical charts and relied on diagnoses present at the time of ovarian cancer diagnosis, such as cardiovascular disease (62). The Dutch study (data extracted from medical records) used a modified Charlson Comorbidity index, defining comorbidity as diseases present at the time of cancer diagnosis (99). Different coding schemes may explain the divergent findings. Information from medical records reflects clinical information and is detailed, but often with a variable quality across sites of care and time (64). It also is possible that ovarian cancer may not be consistently diagnosed in all countries among women with severe comorbidity.

Study V confirmed the result of study IV using nationwide data from the DCR and extended the study by including information on stage. These findings were in agreement with results of two other cohort studies, in which borderline tumours were excluded (95;96). O'Malley et al. studied, in a population-based setting, 1,051 American women with surgically treated ovarian cancer of FIGO-stage IC or higher, and found decreased survival associated with comorbidity; the MRR for patients with any comorbid condition was 1.4 (95% CI, 1.1-1.7) compared with patients without comorbidity (95). The MRRs were adjusted for stage, but

there was no assessment of the variability of effect by stage. Similarly, in a cohort study in Germany, Du Bois et al. found that comorbidity was an independent prognostic factor [hazard ratio=1.77 (95% CI, 1.23-2.54)] (96). Piccirillo et al. (97) likewise found a negative effect of comorbidity on survival from gynaecologic cancers, although no separate analysis was conducted for ovarian cancer.

Our data contradict the population-based cohort study in The Netherlands by Mass et al. (99), which was restricted to approximately 500 ovarian cancer patients with FIGO-stage II and III. Mass et al. used a slightly modified Charlson Comorbidity Index and adjusted for treatment, age, stage, and calendar period of diagnosis, but failed to show a prognostic value of comorbidity. Other cohort studies likewise found no prognostic impact of comorbidity (28;98;100). The Norwegian (N=571) population-based cohort study examined the impact of several possible prognostic factors on survival and found a prognostic impact of comorbidity in the univariate analysis, but the association disappeared after adjusting for age, stage, grade, histology, residual tumour, teaching hospital, CA-125 and calendar time (28). We did not adjust for all these possible confounding factors, which may explain an apparent association in our study. Presence of a residual tumour is related to the aggressiveness of surgery and if comorbidity results in less aggressive surgery, residual tumour may be an intermediate in the causal pathway from comorbidity to death. In this situation, adjustment for residual tumour would be inappropriate. The effect of comorbidity on mortality may be mediated to a large degree by higher volume of residual tumour.

A Dutch population-based cohort study (N=1,116) adjusted for stage, treatment and age, but did not find an association between comorbidity and mortality (100). An American hospital-based cohort study (N=137) found an age- stage- and symptom stage-adjusted MRR of 1.04 in ovarian cancer patients with comorbidity compared with ovarian cancer patients without comorbidity (98). Both studies extracted data on comorbidity from medical records with the potential associated limitations (64). Further, the American study was very small, possibly including highly selective patients, given that only 137 patients were included over almost 6 years. None of the earlier studies on comorbidity and ovarian cancer reported whether the impact of comorbidity varied by stage.

Study V confirmed and extended the findings reported in another study for other groups of cancer patients i.e. those with breast cancer, prostate cancer, colon cancer, and lung cancer (139). As in that study, the impact of comorbidity in our study varied by stage.

The presence of comorbidity in a cancer patient may influence the cancer treatment and therefore affect prognosis and survival (100;140). Not all patients with comorbidities receive

standard treatment (99). It is, however, possible that the best strategy for patients with co-morbidity is not to follow the established guidelines for treatment (60) either because they are too fragile for the adjuvant chemotherapy necessary after surgery or because the drugs used to treat their comorbid diseases interact with chemotherapy agents. Further consideration in the use of chemotherapy is that its toxicity may be exacerbated by the side effects of the drugs that are used to treat comorbidities (141). In the DCR there was no valid information on the aggressiveness of the surgery performed or whether a modification of chemotherapy was used. However, adjustment for treatment in the analyses did not remove the variation in the MRR measuring the association between severe comorbidity (Charlson score 3+) and the one-year mortality. Even though we adjusted for treatment, there still could be some differences in the aggressiveness of treatment in the comorbidity groups, as was demonstrated in the Norwegian study (28).

We examined all-cause mortality. Ovarian cancer patients could die from comorbidity or from other causes, possibly unrelated to ovarian cancer. This may partially explain the higher mortality among patients with comorbidity. O'Malley et al. used death from ovarian cancer as the outcome and still found an association with comorbidity (95). We found it difficult to distinguish between the contributions to mortality from the ovarian cancer itself and that from cancer complications or comorbidities. For instance, it can be difficult to distinguish between death from heart disease and death caused by chemotherapy-related aggravation of existing cardiac problems.

7 Main conclusions

7.1 Study I

The hospital discharge diagnosis was of high quality and could provide up-to-date survival estimates and serve as a system for the departments to monitor the effectiveness of the clinical care of ovarian cancer patients. However, the data (ICD-10) in the regional HDR had errors, primary represented by classification of borderline tumours as ovarian cancer, and the stage-specific ovarian cancer codes were not consistently used. Further, we found that the regional HDR data did not allow separation of borderline tumours from invasive ovarian cancer. Such misclassification could bias absolute survival estimates, however, since PPV was high, the relative survival estimates are expected to be unbiased. The misclassification was found to have little impact on survival estimates. Thus, the regional HDR can be a valuable tool for future research of ovarian cancer.

7.2 Study II

This study provided the reassuring finding that the survival of ovarian cancer patients has improved in Denmark in the latest decades. However, the survival after ovarian cancer remained poorer than in other countries. This change was most pronounced in women older than 40 years.

7.3 Study III

Ovarian cancer diagnosed less than four months after VTE was associated with an advanced stage, and the prognosis for such patients tended to be poorer than for ovarian cancer patients without VTE. These observed differences in mortality may arise from real differences in the prognosis of ovarian cancer patients with and without VTE, but might also be influenced by the biology of the ovarian cancers associated with VTE. Our findings may have implications for the clinical care of ovarian cancer patients with prior VTE.

7.4 Study IV

One quarter of ovarian cancer patients had at least one recorded comorbid disease, and five percent had severe comorbidity. Severe comorbidity was a predictor of reduced survival in Danish women with ovarian cancer. We found improvement in survival over time in patients without recorded comorbidity, whereas survival in patients with comorbidity remained essentially unchanged. The increased mortality can be explained by comorbidity itself, or by the

fact that patients with comorbidity may be diagnosed with advanced disease; it is also possible that ovarian cancer patients with comorbid conditions receive less aggressive treatment.

7.5 Study V

The presence of severe comorbidity in ovarian cancer patients was associated with an advanced stage. The mortality was higher among patients with comorbidity than among those without comorbidity even after adjustment for stage. The impact of comorbidity on ovarian cancer survival varied by stage, with a higher mortality in patients with tumours with regional spread/FIGO-stage II and III tumours.

8 Perspectives

We found that the overall survival of ovarian cancer improved over time, although for unknown reasons survival is still lower in Denmark than in other countries. Thus, attention is needed to further improve the survival. We showed that the regional HDR can provide updated data to be used for monitoring ovarian cancer survival in Denmark, even at department level. Prognostic factors, such as an episode of VTE within 4 month before the ovarian cancer diagnosis and presence of severe comorbidity have negative impact on survival of ovarian cancer. Conversely, since we only identified few cases of ovarian cancer following VTE, this is practically not a major clinical problem.

To improve the prognosis of ovarian cancer in Denmark the focus should be on:

- early and improved diagnostics (including knowledge about comorbidity)
- improved treatment and implementation
- improved clinical performance at the individual level and the systemic level (organisation)
- improved patient compliance

Interventions like the above require monitoring of the effect and feedback to the implicated parts in order to improve survival. In the future, we expect that the regional HDR will be an even more valuable tool in research and in monitoring ovarian cancer survival, first of all because the misclassification of ovarian cancer is expected to diminish, mainly because a code for borderline tumours has been established as of April 1 2007. Secondly with a higher focus on the importance of using the stage specific ICD-10 ovarian cancer codes by the physicians, stage information is expected to improve in the future.

Our findings suggest that it is important to broaden the diagnostics of ovarian cancer to include comorbidity of the patients. Using Charlson Comorbidity score based on previous discharge diagnoses in HDR is a possible way to take comorbidity into consideration when studying prognosis of ovarian cancer.
Improvement of the treatment is an important issue for all ovarian cancer patients - also patients with comorbidity. A comprehensive assessment of comorbidity should be incorporated into the preoperative evaluation to permit a tailored approach to perioperative care. In future research, we will examine to which extent comorbidity influences the choice of treatment in ovarian cancer patients. To further investigate this, we need to obtain detailed information on surgery and chemotherapy from hospital medical records and the clinical database (DGCD).

Recently it has been debated whether a centralisation of ovarian cancer treatment could improve survival of ovarian cancer. For example, in 2004, surgery for ovarian cancer in Denmark took place in 52 hospital departments (142). However, this number is probably too high since it also included departments who unexpectedly found ovarian cancer in patients that not a priory was expected to have ovarian cancer. Any reorganisation of the treatment should be monitored in the future. The HDR would thus be a valuable tool in monitoring the effect of centralising the treatment of ovarian cancer taking comorbidity into account.
We found no information on patient compliance for ovarian cancer patients; however patients' refusal of surgery or chemotherapy may have impact on survival of ovarian cancer and needs further examination.

9 Summary

Cancer of the ovary has been described as a "silent killer" because the majority of patients do not present with symptoms until the disease has spread outside of the ovary and sometimes outside of the pelvis. Ovarian cancer is a disease primarily occurring in elderly women, of whom some may have coexisting diseases. Ovarian cancer will therefore remain a public-health burden in the future.

Denmark has one of the highest ovarian cancer mortality rates, underscoring the need for quality assurance systems to monitor effectiveness of the treatment with updated data. Further, in order to improve survival after ovarian cancer we need better understanding of the disease itself, including knowledge about prognostic factors that can be acted upon for prevention.

This thesis is based on five epidemiologic studies built on data from the Danish Cancer Registry, the Hospital Discharge Registry of North Jutland County, the National Hospital Discharge Registry, the County Pathology Registry (Aalborg), and the Civil Registration System.

The aims of the thesis were to examine 1) the quality of the ovarian cancer diagnosis in the updated County Hospital Discharge Registry and to quantify the impact of misclassified diagnoses on survival estimates; 2) ovarian cancer survival, from 1985 to 2004; 3) the impact of prior venous thromboembolism (VTE) on survival; and 4) impact of comorbidity on ovarian cancer survival while taking tumour stage into consideration.

In **study I**, we found the hospital discharge diagnosis to be of high quality and able to provide updated survival estimates and to serve as a system for the departments to continuously monitor the effectiveness of the clinical care of ovarian cancer patients. The completeness was 96% (95%CI, 94%–98%) and the positive predictive value was 87% (95%CI, 85%–90%) when we used the Danish Cancer Registry (including borderline tumours) as the reference standard. The main type of misclassification in the regional HDR was categorising borderline tumours as ovarian cancer. This misclassification had, however, no major impact on survival estimates.

In **study II**, we have shown the improvement in the overall survival 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 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 who were older than 40 years.

In **study III**, we identified 128 ovarian cancer patients with prior VTE out of 12,835 ovarian cancer patients diagnosed from 1980 to 2003 in the DCR. Of these, 50 patients were diagnosed with ovarian cancer within 4 months after the VTE and 78 patients were diagnosed more than 4 months after the VTE diagnosis. Advanced tumour stages tended to be found more often among patients with VTE. One-year MRR adjusted for age, calendar time, comorbidity, and FIGO-stage were 1.7 (95% CI, 1.2–2.5) for ovarian cancer patients diagnosed less than 4 months after the VTE and 1.2 (95% CI, 0.8–1.7) for ovarian cancer patients diagnosed more than 4 months after the VTE diagnosis.

In **study IV**, we found that the proportion of ovarian cancer patients without comorbidity fell from 81% to 75% during the study period, while the proportion of patients with comorbidity score 1-2 and 3+ rose. Overall one-year survival increased from 68% in 1995-1997 to 73% in 2001-2004. This improved survival was mainly seen in patients without comorbidity, whereas survival in patients with comorbidity remained largely unchanged. Among patients with severe comorbidity (Charlson score 3+) the mortality was approximately twice as high as in patients without comorbidity.

In **study V**, comorbidity was more common among patients with advanced tumour stage. The one- and five-year survival was higher in patients without comorbidity than in patients with registered comorbidity. After adjustment for age and calendar time, the one-year MRRs declined from 1.8 to 1.4 and from 2.7 to 2.0 for Charlson score 1-2 and 3+, respectively. Further adjustment for stage caused MRRs to decline further, to 1.3 and 1.8. The impact of severe comorbidity on mortality varied by stage, with the most pronounced effect observed among patients having tumours with regional spread/FIGO-stage II and III.

We conclude that ovarian cancer data available as discharge diagnoses are of high quality and suitable for monitoring survival, despite the misclassification of patients with borderline tumours. The hospital discharge data were used in study II, and showed that ovarian cancer survival has improved over time. Further, we found that ovarian cancer patients diagnosed within four months after an episode of VTE were associated with an advanced stage and a poor prognosis. In the last two studies, we found that one quarter of Danish women with ovarian cancer had comorbidity, and 5% had severe comorbidity. Overall survival improved

over time in patients without comorbidity, whereas no improvement was seen in patients with comorbidity. Severe comorbidity was a predictor of poor survival independently of tumour stage.

10 Danish summary

Ovariecancer er blevet beskrevet som en "silent killer" fordi de fleste patienter ikke viser symptomer før sygdommen har spredt sig uden for ovarierne og endda nogle gange udenfor det lille bækken. Ovariecancer forekommer overvejende hos ældre kvinder, som også kan have andre sygdomme. Ovariecancer vil derfor fortsat være en byrde i fremtiden.

Danmark har en af de højeste dødeligheds rater af ovariecancer i verden, hvilket understreger nødvendigheden af kvalitetssikringssystemer for at kunne monitorere effekten af den terapeutiske indsats ved hjælp af opdaterede data. For at forbedre overlevelsen af ovariecancer er vi nødt til at få en bedre forståelse af sygdommen og de faktorer, der kan have betydning for overlevelsen, således at vi kan intervenere mod dem.

Denne afhandling er baseret på 5 klinisk epidemiologiske studier byggende på data fra Cancerregistret i Danmark, det patient administrative system (PAS) i Nordjyllands, Viborg, Århus og Ringkøbing amter, Landspatientregistret (LPR), det lokale patologi register (Aalborg) og CPR registret.

Formålene ved Ph.d. studiet var 1) at undersøge datakvaliteten af ovariecancer diagnosen i PAS samt at vurdere hvilken betydning en eventuel misklassifikation havde på overlevelsesestimater, 2) at undersøge overlevelsen af ovariecancer fra 1985 til 2004, 3) at undersøge betydningen af tidligere tilfælde af dyb venetrombose (DVT) for overlevelsen af ovariecancer, og 4) at belyse sammenhængen mellem tilstedeværelse af komorbiditet og overlevelse af ovariecancer, stadiet taget i betragtning.

I **studie I** fandt vi, at udskrivnings diagnosekoder for ovariecancer fra PAS var af høj kvalitet og PAS kunne levere opdaterede data til analyser af ovariecancer overlevelse, og kunne bruges som et monitorerings system på afdelingsniveau til at monitorere effektiviteten af den kliniske behandling af ovariecancer patienterne. Komplethedsgraden var 96% (95%CI, 94%–98%), og den positive prædiktive værdi var 87% (95%CI, 85%–90%), når vi brugte Cancer Registeret (inklusive borderline tumorer) som reference. I PAS var ovariecancer i visse tilfælde misklassificerede, det var primært borderline tumorer, der var klassificeret som ovariecancer. Denne misklassifikation havde dog ikke større betydning for overlevelsesestimaterne.

I **studie II** fandt vi en forbedret overlevelse af ovariecancer i perioden 1985-2004. Etårs overlevelsen steg fra 61% til 73%, og femårs overlevelsen fra 30% til 38%. I forhold til pe-

rioden 1985-1989 var den aldersjusterede etårs mortalitets rate ratio (MRR) 0,65 (2000-2004) og aldersjusteret femårs MRR 0,80 (1995-1999). Forbedringen var størst hos patienter ældre end 40 år.

I **studie 3** identificerede vi 128 ovariecancer patienter med tidligere dyb venetrombose ud af 12,835 ovariecancer patienter diagnosticeret fra 1980 til 2003 i Cancerregisteret. Af disse var 50 patienter diagnosticeret med ovariecancer inden for 4 måneder efter episoden med DVT og 78 patienter var diagnosticeret mere end 4 måneder efter en episode med DVT. Avanceret stadier blev oftere fundet hos patienter med DVT. Ovariecancer diagnosticeret mindre end fire måneder efter DVT var associeret med avanceret stadie og en dårlig prognose. Et-års MRR (justeret for alder, kalendertid, komorbiditet og stadie) var 1.7 (95% CI, 1.2–2.5) for ovariecancer patienter diagnosticeret indenfor 4 måneder efter en episode med DVT og 1.2 (95% CI, 0.8–1.7) for ovariecancer patienter diagnosticeret mere end 4 måneder efter en episode med DVT.

I **studie 4**, fandt vi at andelen af ovariecancer patienter uden komorbiditet faldt fra 81% til 75% i løbet af studie perioden, mens andelen af patienter med komorbiditets score 1-2 og 3+ steg. Den samlede et-års overlevelse steg fra 68% i 1995-1997 til 73% i 2001-2004. Denne forbedring så man primært hos patienter uden komorbiditet, hvorimod overlevelsen hos patienter med komorbiditet forblev uændret. Hos patienter med svær komorbiditet (Charlson score 3+) var dødeligheden ca. dobbelt så stor i forhold til patienter uden komorbiditet.

I **studie 5** blev komorbiditet oftere fundet hos patienter med avanceret stadie af ovariecancer. Et og fem-års overlevelsen var højere for patienter uden komorbiditet i forhold til ovariecancer patienter med registreret komorbiditet. Når vi justerede for alder og kalendertid faldt et-års MRR fra 1.8 til 1.4 for Charlson score 1-2, og fra 2.7 til 2.0 for Charlson score 3+. Hvis vi yderligere justerede for stadie faldt MRR til henholdsvis 1.3 og 1.8. Betydningen af svær komorbiditet varierede i forhold til stadiet, hvor den største effekt blev observeret hos patienter med regional spredning af tumor/FIGO-stadie II og III.

Sammenfattende fandt vi at PAS/LPR var velegnet til at monitorere og studere overlevelse af ovariecancer til trods for misklassifikation af patienter med borderline tumorer. Overlevelsen blev bedre over studie perioden, men var stadig dårligere end i andre lande. DVT inden for 4 måneder før canceren blev diagnosticeret var associeret med avanceret stadie og en dårlig

prognose. I de sidste to studier fandt vi at en fjerde del af danske ovariecancer patienter havde komorbiditet og 5% havde svær komorbiditet. Overlevelsen blev forbedret over tid for de patienter der ikke havde komorbiditet, mens ingen forbedring blev set hos de patienter, der havde komorbiditet. Svær komorbiditet havde negativ betydning for overlevelsen af ovariecancer uden at dette kunne forklares af stadiet.

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12 Appendix

Translation of disease categories in the Charlson Comorbidity Index into discharge diagnoses in ICD-8 and ICD-10.

Diseases	ICD8	ICD10
Myocardial infarction	410	I21;I22;I23
Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2
Peripheral vascular disease	440; 441; 442; 443; 444; 445	I70; I71; I72; I73; I74; I77
Cerebrovascular disease	430-438	I60-I69; G45; G46
Dementia	290.09-290.19; 293.09	F00-F03; F05.1; G30
Chronic pulmonary disease	490-493; 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Connective tissue disease	712; 716; 734; 446; 135.99	M05; M06; M08; M09;M30;M31; M32; M33; M34; M35; M36; D86
Ulcer disease	530.91; 530.98; 531-534	K22.1; K25-K28
Mild liver disease	571; 573.01; 573.04	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0
Diabetes type1 Diabetes type2	249.00; 249.06; 249.07; 249.09 250.00; 250.06; 250.07; 250.09	E10.0, E10.1; E10.9 E11.0; E11.1; E11.9
Hemiplegia	344	G81; G82
Moderate to severe renal disease	403; 404; 580-583; 584; 590.09; 593.19; 753.10-753.19; 792	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61
Diabetes with end organ damage type1 type2	 249.01-249.05; 249.08 250.01-250.05; 250.08	 E10.2-E10.8 E11.2-E11.8
Any tumour	140-194	C00-C75
Leukaemia	204-207	C91-C95
Lymphoma	200-203; 275.59	C81-C85; C88; C90; C96
Moderate to severe liver disease	070.00; 070.02; 070.04; 070.06; 070.08; 573.00; 456.00-456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85
Metastatic solid tumour	195-198; 199	C76-C80
AIDS	079.83	B21-B24