Register studies of cancer in the Southern Health Care Region in Sweden

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CONTENTS

1 ABSTRACT

Aim: The overall aim of this thesis was to study different aspect of health, health care and health care costs on a population based level for persons with cancer and their partners, and from an individual level to explore the impact of comorbidities in incidence and survival. The aim was also to provide methods and platforms for continuous follow-up of care initiatives and results in the total episode of care especially with extent of tumour diseases and comorbidities.

Material and Methods: In the beginning of the study all persons in the Health Care Region in Sweden diagnosed with colon, rectal, breast, prostate and lung cancer during the period 2000 to 2005 were identified via the Swedish Cancer Register. Only data for patients with invasive tumours were included. The obtained information was on an individual level linked by the ten digit personal identification number to other population based registries as the Swedish Population Register and health care registries for Sweden and Skåne. The date of the cancer diagnosis for the patient was chosen to be the date of the diagnosis for the partner and therefore chosen to be the time point for comparison of outcomes before and after. In the first study health care use, diagnoses and health care costs were analysed for partners to patients in Skåne (n=11,076). In the third study, data of health care costs were presented for both patients with prostate cancer (n=7,319) and their partners (n=4,860) and then also using information from the Regional Prostate Cancer Register in Southern Sweden to analyse data of treatment for patients.

Lately in the study we identified all persons diagnosed with cancer including the period 2006 to 2007 in the same way and analysed all types of cancer with specification of 18 types of cancer. Comorbidity diagnoses for patients (n=19,756) and all data for up to 8 eight control persons (n=147,324) were also extracted from health care registries in Skåne. In the second study the correlation between dementia and cancer was presented with a risk time period of 9-45 months depending on the date of diagnosis of the cancer patient and in the fourth study based on the same data, the correlations between diabetes, obesity or abnormal blood lipids and cancer were presented but also including a complementary longer risk time period, up to ten years, excluding some patients (n=19,058) and controls (n=141,333).

In the fifth study we combined information from the whole study and presented data of health care costs for patients with lung cancer diagnosed during the period 2000 to 2005 (n=2,920) and their partners (n=1,488), as well as in the second study for prostate cancer, but we could only analyse data of treatments for the period 2002 to 2005 using information from the Regional Lung Cancer Register in Southern Sweden. Survival for patients with non-small cell lung cancer 2000-2007 in the Southern Health Care Region was also presented (n=2,726).

Results: The major part of health care costs for prostate and lung cancer patients occurred during the first year following the diagnosis. A clear difference was seen between costs for survivors and patients who later died. For patients with prostate cancer health care costs increased with higher Gleason score in the year following the diagnosis. Higher health care costs were seen for patients treated with primary radiotherapy and lowest costs were seen for patients with expectancy. Health care costs were higher for patients with curative treatments compared to those with palliative treatments. For patients with lung cancer the costs totally were declining with higher stage. Highest health care costs were seen for patients treated with endoscopic therapy of the bronchus. Health care costs were higher for operated patients compared to those with treatments only by chemotherapy or radiotherapy.

Higher survival in patients with NSCLC was explained by surgery, short waiting time, treatments by chemotherapy or radiotherapy and patients living in a specific geographic area. Lower survival was connected to no treatment, tumour stage, performance status and alcoholic related diseases.

Overall a diagnosis of dementia was significantly less common among the cancer cases (RR=0.60, 95% CI=0.52–0.69). Diabetes was significantly more common prior to diagnosis in patients with liver, pancreatic, colon and urinary tract/bladder cancer and in patients with breast cancer diagnosed with diabetes 0–4 years prior to the cancer diagnosis. A lower risk of diabetes was seen in patients with prostate carcinoma among individuals with diabetes diagnosed 5–10 years prior to the cancer diagnosis. The findings remained after adjusting for obesity and high blood lipids. Obesity was significantly more common in patients with endometrial, colon and kidney cancer and with breast cancer above the age of 60 years in those where obesity was diagnosed close to the diagnosis of cancer. High blood lipids were significantly more common in patients with ovarian cancer and less common in patients with breast cancer.

Health care consumption and health care costs for partners increased in the years following the cancer diagnosis of the person with cancer especially for partners to colon, prostate and lung cancer patients with highest figures for younger male partners (age 25-64 years) of patients with colorectal and lung cancer. The number of diagnoses increased significantly among partners in the whole sample (RR=1.24, 95% CI=1.21-1.24) with the largest increase in psychiatric diagnoses (RR=2.02, CI=1.73-2.37).

Conclusions: Lung cancer and prostate cancer are important issues in terms of health care decisions. In this study we have elucidated different perspectives of significance when calculating costs for these types of cancer. In the future, new treatments, especially new pharmacy, are to change the relationship between treatments, costs and survival. In future research this also needs to be considered, as costs of lung cancer are likely to increase. It is of importance also further examine in what way results are affected by how the patient comes in contact with the health care system, the patient´s lifestyle and socioeconomic background or the health care system itself (organisation, competence etc).

The study confirms some previous findings concerning comorbidity and cancer and highlights some new ones. The study confirms previous findings that patients with dementia have a lower risk of cancer. Because the effect was seen for all tumour types and especially for patients older than 70 years and since the deficit was more pronounced for patients with tumours situated within the body, the data suggest that malignancies are underdiagnosed for persons with dementia. From a public health view avoiding overweight and obesity, as well as preventing type II diabetes mellitus, are important in preventing cancer and other diseases. Measures should be taken early on and should be based on healthy eating and physical activity patterns throughout life. Obesity, diabetes mellitus and blood lipid abnormalities are important comorbidities for distinct cancer forms and their prevention could have a substantial health impact on cancer and non-cancer diseases. Furthermore, this new knowledge concerning cancer and comorbidities may provide an insight into the mechanisms of tumour development. Postponing the onset of comorbidity may also prevent/postpone the diagnosis of cancer.

Further research is needed to learn more about the situation of the partner and to identify persons at risk of psychiatric morbidity. Knowledge is also needed on how to support the partner in the most efficient way. When planning for care and allocation of resources for care the impact on the partner should also be considered.

2 DEFINITIONS AND ABBREVIATIONS

Person with cancer and cancer patient
The terms *person with cancer* and *cancer patient* are in this thesis used to refer to the person that has been diagnosed with cancer.

Partner
Partner is in this thesis defined as spouse or partner living together at the same address as the person with cancer at the time for the cancer diagnosis.

ABC	Activity Based Costing
CI	Confidence interval
DRG	Diagnose Related Group
HR	Hazard ratio
ICD 10	International Statistical Classification of Diseases and Related Health Problems 10th Revision for 2007
KVÅ	Klassifikation av vårdåtgärder (Classification of health-care treatments/activities)
NSCLC	Non-small cell lung cancer
PSA	Prostate Specific Antigen
RCC	Regional Cancer Centre
RR	Relative risk (risk ratio)
SCR	Swedish Cancer Register
SRHCC	Southern Regional Health Care Committee
WHO	World Health Organisation

3 ORIGINAL PAPERS

This thesis is based on the following papers, which are referred to in the text by their Roman Numerals (I-V)

I Sjövall K.*, Attner B.*, Lithman T., Noreen D., Gunnars B., Thomé B. and Olsson H. (2009). Influence on the health of the partner affected by tumour disease in the wife or husband – A population based register study of cancer in Sweden. Journal of Clinical Oncology 27 (28): 4781–6

*These authors Contributed Equally

II Attner B, Lithman T, Noreen D, Olsson H (2010). Low cancer rates among patients with dementia in a population–based register study in Sweden. Dement Geriatr Cogn Disord.30(1):39–42

III Sjövall K*, Attner B*, Lithman T, Noreen D, Olsson H (2011) Prostate Cancer in the Pre and Post Diagnosis Phase – A Population Based Study on Health Care Costs. Epidemiol S1:001

*These authors Contributed Equally

IV Attner B, Landin–Olsson M, Lithman T, Noreen D, Olsson H (2012) Cancer among Patients with Diabetes, Obesity and Abnormal Blood Lipids – a Population–based Register Study in Sweden. Cancer Causes Control (2012) 23:769–777 Epub 2012 March 31.

V Attner B, Sjövall K, Lithman T, S-B. Ewers, L. Ek, Noreen D, Olsson H (2012) A population-based study of health care costs for patients and partners with lung cancer and of factors influencing survival in patients with non-small cell lung cancer (NSCLC) in Sweden. *Submitted*

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This thesis is also supported by the following reports and articles, which are referred to in the text by their Roman Numerals (VI-VIII)

VI Attner B., Lithman T., Noreen D., Olsson H. Registerstudier av cancersjukdomar i Södra sjukvårdsregionen. Rapporter Etapp 1–4, Södra sjukvårdsregionen 2008–09, http://www.skane.se/templates/Page.aspx?id=208634

VII Sjövall K., Attner B., Lithman T., Noreen D., Gunnars B., Thomé B., Olsson H., Lidgren L., and Englund M. (2010) Sick leave in spouses to cancer patients before and after the diagnosis. Acta Oncol. May;49(4):467–73.

VIII Sjövall K, Attner B, Englund, M Lithman T, Noreen D, Gunnars B, Thomé B, Olsson H and, Petersson I F. (2011) Sickness absence among cancer patients in the pre-diagnostic and the post-diagnostic phases of five common forms of cancer. Supportive Care in Cancer, published online 10 April 2011.

4 INTRODUCTION

Focus on cancer has extremely increased both in Sweden and in the rest of the world. The Swedish national cancer strategy for the future was presented 2009 (and introduced 2010) with the prognosis that the prevalence of cancer in Sweden will increase with 100% from period 2002-2006 to 2030, for men and women with 130% and 70% respectively (1) . The situation is more or less the same in Europe and the rest of the world with increasing number of individuals that are diagnosed with cancer and with a growing number of people surviving cancer or living for prolonged time periods with the disease (2-12)

The Southern Regional Health Care Committee (SRHCC) had already 2004 initiated a study of the process for the provision of cancer health care in southern Sweden. The aim was to examine and analyse incidence, health care consumption, outcomes and costs among persons with common types of cancer including colon, rectal, lung, breast, or prostate cancer. Results have been presented in four reports 2008-2009, (13)

Few studies have used a population-based approach and healthcare consumption, outcome and costs on an individual level have seldom been studied (14, 15) . Studies of the influence of comorbidity on the incidence and survival rates for cancer have often focussed on one cancer form and on one comorbidity at a time and have mostly been in form of cross-sectional and case–control studies. Register-based studies have often used only inpatient data leading to an underestimation of the comorbidity itself. Recently the "Review of methods used to measure comorbidity in cancer populations: No gold standard exists" was presented (16). No golden standard approach to measuring comorbidity in the context of cancer exists. Approaches vary in their strengths and weaknesses, with the choice of measure depending on the study question, population studied, and data available.

A lot of studies have pointed out different factors influencing survival in cancer (3, 8, 11, 17-35), both in common and for different types of cancer. Improved treatment methods have in common increased survival rates with additional health care costs. Baker et al (36) already 1991 presented assigned costs associated with each cancer to three post diagnostic time periods: 1) initial treatment, during the first three months following diagnosis 2) maintenance care, between initial and terminal treatment; and 3) terminal treatment during the final six months prior to death. Recently Krahn et al has presented results showing that costs are highest around two events, the cancer diagnosis and cancer death (37).

In another recent published article, "Cost efficiency of university hospitals in the Nordic countries: a cross-country analysis" presents significant differences in university hospital cost efficiency when variables for teaching and research are entered into the analysis, both between and within the Nordic countries. The results of a second-stage analysis show that the most important explanatory variables are geographical location of the hospital and the share of discharges with a high case weight. However, a substantial amount of the variation in cost efficiency at the university hospital level remains unexplained. Cost of Cancer in the Nordic countries is a recent SINTEF-study presenting that cancer-related treatment costs can be expected to increase by 28 per cent by 2025 due to increasing cancer prevalence in the future. This estimate does not take into account future changes in treatment costs due to innovations in technology, cancer therapy and organization of treatment and is therefore likely to be on the low side. The rising costs of cancer treatment raise important questions concerning how to address future challenges including the question of sustainable growth, efficient use of available resources, advances in cancer prevention and treatment, and the impact of financial mechanisms. All our data of cost for treatment in the study were collected before the widespread use of new target therapeutic pharmaceuticals. The cost for these pharmaceuticals has been increasing rapidly in recent years. Our data, therefore, provide a baseline for further studies of the effects of the new targeted therapy.

5 BACKGROUND

5.1 Cancer and inequalities in health in the Southern Health Care Region in Sweden

5.1.1 The Swedish health care system, the cancer strategy and the role of the Southern Regional Health Care Committee

Sweden, with a population of 9.5 million inhabitants (2012-05-31), is divided in 21 counties, 23 county councils and 290 municipalities. All county councils and municipalities have their own self-governing local authority and are mostly funded by taxes. The health services in Sweden are a public matter and the main task of the county councils is health care.

Sweden is also divided in six health care regions. The Southern Health Care Region consists of the county councils of Skåne, Blekinge, Halland (south) and Kronoberg with a total population at nearly 1.7 million inhabitants. The region has a board of politicians, the Southern Regional Health Care Committee (SRHCC). The aim for the committee is, with incomes from the involved county councils, to coordinate special tasks in the health-care. One example is the "The Regional prize-list" that regulates how one county council will be paid when a patient from another county council visits primary care or gets different treatments in hospital. Other examples are coordination of knowledge management and different projects about prioritizing and equality in health care (www.srvn.org).

The committee initiated a study of the process for the provision of cancer health care in southern Sweden. The aim was to examine and analyse incidence, health care consumption, outcomes and costs among persons with common types of cancer including colon, rectal, lung, breast, or prostate cancer. The first report published in 2008 showed large differences in incidence and survival for patients diagnosed with cancer 2000-2005 due to in which geographical area the patients were living, especially for prostate and lung cancer. Therefore, a wider study with longer time period (2000-2007) was done 2009 analysing all types of cancer and with specification of 18 types of cancer. In the meanwhile two other reports were done to analyse the patient´s visits to doctors before and after the patient got the cancer diagnosis and whether other diagnoses/comorbidities were associated with the diagnosis of cancer (13)

The Swedish national cancer strategy for the future (1) was presented 2009 and has been introduced in February 2010. In the document states that a strategy needs to have clear goals to drive implementation and to enable an assessment to be made of whether the intended effects have been attained. Therefore the authors have proposed five overall goals for the strategy.

These are to
1. reduce the risk of developing cancer
2. improve the quality of cancer management
3. prolong survival times and improve quality of life after a cancer diagnosis
4. reduce regional differences in survival time after a cancer diagnosis
5. reduce differences between population groups in morbidity and survival time

An important objective of the national cancer strategy is to develop six regional associations, Regional Cancer Centres (RCC), in each of the six health care regions in Sweden.
The leading areas of work for RCC are (1)

- Prevention and early detection of cancer
- Health care processes
- Psychosocial support, rehabilitation and palliative care
- The patient´s role during the management of the disease
- Education/medical training and supplying competence

- Knowledge management
- Clinical cancer research and innovation
- A role of leadership, collaboration and to follow-up the quality of the cancer health care
- A strategic plan to develop the cancer care in the health care region
- Structuring of levels in cancer health care

The RCCs are also expected to collaborate, with each other as well as with similar organisations in other countries. The RCCs shall use information from health care registers, quality registers, and other population based registers for quality control and research. Our data in the study provide a baseline for further studies of the effects of the new targeted therapy and other new treatments. One important question for the future is how to prioritize limited resources and how to move resources from treatment to prevention.

5.1.2 Cancer

5.1.2.1 An overview

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. Today, millions of people all over the world are living with cancer or have had cancer. In most cases, the cancer cells form a tumour. Not all tumours are cancer. Tumours that are cancer are called *malign,* the others are called *benign.* (38).

During 2010 there were 55 342 cases of malignant cancers diagnosed and reported to the Swedish Cancer Registry; 52 per cent of them in men and 48 per cent in women. During the last two decades the average annual increase in number of cases has been 2.0 per cent for men and 1.4 per cent for women. The increase is partly explained by the ageing population but also by the introduction of screening activities and improvements in diagnostic practices (39) .

In Sweden almost 400 000 people were survivors of a cancer diagnosis 2008 (prevalence). They had been diagnosed between 1958 and 2008 and were either cured or still living with the cancer disease (12). The Swedish national cancer strategy (1) was presented with the prognosis that the prevalence of cancer in Sweden will increase with 100% from the period 2002-2006 to 2030, for men and women with 130% and 70% respectively. These figures are explained mostly by a dramatically demographic change with aging population, for men with 55% and for women with 48.5%. Better survival rates and shifting panorama of diagnoses explains for men and women 40% and 41.5% respectively and finally the change in incidence only represents 5% for men and 10% for women. The increase in incidence and prevalence is similar to the development in other European countries and in parts of the rest of the world (2-12).

The most common types of cancer in the Western world are colon, rectal, breast, prostate and lung cancer. In Sweden these types of cancer together account for about 50 % of all cancer (39). The samples in paper I are based on persons with these types of cancer and they are therefore briefly presented below. Breast and prostate cancer are the most prevalent types for women and men respectively (39). As symptoms and treatment methods for colon and rectal cancer are very similar, they are often handled as one diagnosis in the literature. In this overview they are presented as one diagnosis but in paper I-II and paper IV, they are handled as two separate diagnoses. The samples in paper III and paper V are based on prostate and lung cancer respectively and for these types of cancer there is some additional information. Finally, the samples in paper II and IV are based on all types of cancer with specification of 18 types.

5.1.2.2 Colorectal cancer

Cancer of colon and rectum are among the most common types of cancer in Sweden in both males and females and the trend is rather stable although colon cancer in women has increased with 1.4 per cent per year on average during the last decade. Almost 6000 people are every year diagnosed with colorectal cancer in Sweden, and about 75% of them are older than 65 years. The disease is about equally usual among men and women (39).

Developed treatment methods have improved survival rates in the last decade, but there is still a 40-45 % mortality rate within the first five years (1, 13). Primary colorectal cancer it treated with surgery sometimes combined with chemotherapy and/or radiotherapy. During the last decade the development of chemotherapy pharmaceuticals and, so called targeted pharmaceuticals have increased options of treatment methods, especially for persons with advanced disease (40).

5.1.2.3 Breast cancer

Breast cancer is the most common type of cancer in women, accounting for 30 per cent of diagnosed cases in the same year in Sweden (39). About 7,300 women are diagnosed with this cancer per year (2010), but it is a very rare diagnosis among men. Incidence in women has increased with 1.3 per cent annually during the last 20 years but the increase in the recent 10-year period is weaker with an annual change of 0.9 per cent (39). The median age for diagnosis is above 60 years and about 80% of women diagnosed with breast cancer are post- menopausal. Incidence among persons younger than 30 years are less common among women than among men (12).

Screening and new treatments have improved survival rates substantially, with a five-year survival around 85%. Primary treatment is surgery, often combined with adjuvant intended radiotherapy and/or chemotherapy and sometimes also hormonal treatment. (12)

5.1.2.4 Prostate cancer

Prostate cancer is globally the second most common malignancy in men (6, 24). In Sweden it is the most frequently diagnosed cancer typically a disease of men older than 50 years and represents 33 per cent of the male cases in 2010 (39). The incidence has been increasing, mainly because of an older population and the possibilities for earlier detection of the disease. On average, the incidence has increased by 2.4 per cent annually seen over the last 20 years but in the past five years, the incidence of prostate cancer has slightly decreased. The incidence of prostate cancer is related to the use of screening with Prostate Specific Antigen (PSA) in health care and therefore it is uncertain how the incidence trend will develop over the coming years (6, 24) Survival rates have also improved for men with prostate cancer, and over 70 % survival is estimated after five years (13)but the PSA testing has resulted in several more cases being diagnosed and that has most likely contributed to improved survival. However, there is still a debate about the use of PSA, as it is associated with a risk of diagnosing tumours of low malignancy grade potentially not harming the individual.

The primary treatment for men with prostate cancer is either surgery or radiotherapy. Therapy could also include hormonal manipulations, immune therapy or chemotherapy.
Furthermore, a great number of patients live for a considerable time following the diagnosis as the disease often progresses slowly. Despite declining mortality rates, costs are thus expected to further raise in the future (33).

5.1.2.5 Lung cancer

Lung cancer is the most frequent cause of cancer deaths in the Western world today. Globally, it is estimated that 1.3 million patients die from lung cancer every year and this figure is predicted to rise even more. Thus there is an urgent need for new methods for early detection of this disease. Despite

progress in treatment results during the past decade, the prognosis is poor and also associated with high comorbidity rates (5, 6, 41). Furthermore this cancer diagnosis is associated with the highest prevalence of psychological distress (42).

In Sweden lung cancer is the fifth most diagnosed cancer with about 3500 new cases every year (2009). The incidence is increasing especially among women (39) and nowadays they constitute about 51% due to changing smoking habits the last 50 years. In the southern health care region in Sweden about 50% of the patients are older than 70 years and about 70% are in a late stage of the disease (stage III b-IV) with a one-year survival of barely 40 % and a five-year survival of 12 % (13).

The second most common cause of death in Sweden is neoplasm (23 per cent for women and 27 per cent for men). Among neoplasms, lung cancer is now the most common cause of death among both men and women, (39) and has increased considerably in women since the late eighties; 81 per cent between 1987 to 2007 (12) This situation in Sweden reflects that more and more women started to smoke after 1960, and this increasing came at a later time period than in United States. The Report to the Nation in United States was first issued in 1998. In addition to drops in overall cancer mortality and incidence, this year's report also documents the second consecutive year of decreasing lung cancer mortality rates among women. Lung cancer death rates in men have been decreasing since the early 1990 (4).

The disease is strongly related to smoking and as most persons with lung cancer are former or active smokers, the comorbidity is often high and the rate of survival is low. New treatments and better diagnostics have improved survival in the short term. Surgery, radiotherapy and chemotherapy are all used in different combinations and with different intentions depending on disease stadium (39). Recently various targeted therapies have been added to the treatment.

5.1.3 Factors influencing differences in health

The study was initiated by the Southern Regional Health Care Committee with intentions to find explanations of differences in incidence and survival using ordinary register with continually reported data available in the county councils for following-up care initiatives and results within the total episode of care especially with special reference to the extent of tumour diseases.

What factors can explain the differences in incidence and survival? Comorbid illness is a significant concern in patients with cancer. Recently the "Review of methods used to measure comorbidity in cancer populations: No gold standard exists" was presented (16). No golden standard approach to measuring comorbidity in the context of cancer exists. Approaches vary in their strengths and weaknesses, with the choice of measure depending on the study question, population studied, and data available. Geraci et al have 2005 presented a model to handle comorbidity and cancer (43) and chronic diseases have been reported to be linked with a higher risk of cancer in several articles (7, 25, 26, 44-57).

In a consensus report from 2010, "Diabetes and Cancer" (58) the authors give a statement: "Diabetes and cancer are common diseases that have a tremendous impact on health worldwide. Epidemiologic evidence suggests that people with diabetes are at a significantly higher risk of many forms of cancer. Type 2 diabetes and cancer share many risk factors, but to our knowledge, potential biologic links between the 2 diseases are incompletely understood. Moreover, evidence from observational studies suggests that some medications used to treat hyperglycemia are associated with either an increased or reduced risk of cancer. Against this backdrop, the American Diabetes Association and the American Cancer Society convened a consensus development conference in December 2009. After a series of scientific presentations by experts in the field, the writing group independently developed this consensus report to address the following questions:

1) Is there a meaningful association between diabetes and cancer incidence or prognosis?
2) What risk factors are common to both diabetes and cancer?
3) What are possible biologic links between diabetes and cancer risk?
4) Do diabetes treatments influence the risk of cancer or cancer prognosis?"

These four questions (Q1-Q4) are illustrated in Figure 5.1.

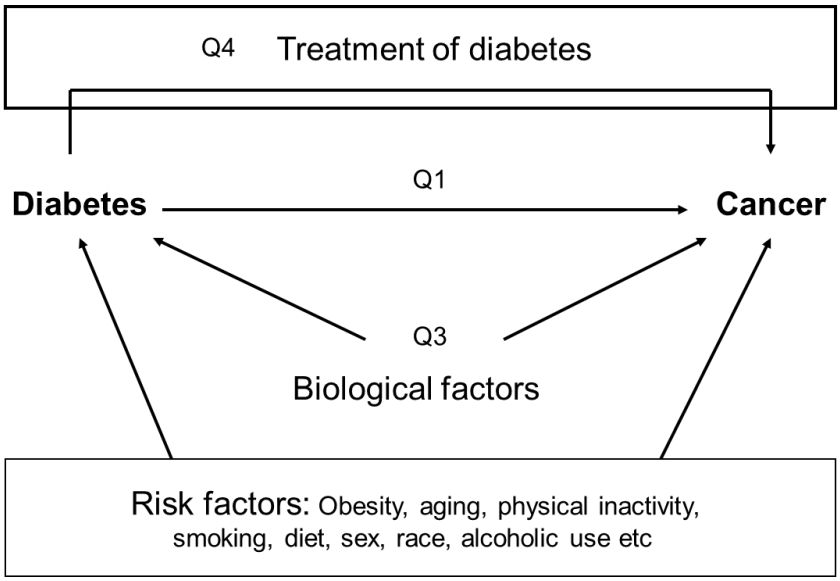

Figure 5.1. Four questions (Q1-Q4) about correlations between diabetes and cancer from the American Diabetes Association and the American Cancer Society (illustration)

These questions could be generalised for different co-diseases and comorbidities. Due to the aging population structure patients generally suffer from additional comorbidities making the model very appropriate. Studies of the influence of comorbidity on the incidence and survival rates for cancer have often focussed on one cancer form and on one comorbidity at a time and have mostly been in form of cross-sectional and case–control studies. Register-based studies have often used only inpatient data leading to an underestimation of the comorbidity itself.

It is a common observation that the overall survival of cancer populations decreases as the burden of comorbid disease increases (3, 7, 11, 21, 23, 25, 26, 28, 35, 46, 56, 58-61). Information provided by this model is useful in estimating the prognosis of individual patients and also in risk stratification for comparison of outcomes.

5.2 Population based records and registries in Sweden

In Sweden population-based records have been established since many years ago. The unique individually personal identification number was introduced in 1947 and in 1967, after that population records were computerised during the 1960´s, a check digit was added. The Swedish Cancer Register was founded in 1958 (39, 62, 63) , covers the whole Swedish population and is administrated by the National Board of Health and Welfare.

According to Regulations by the National Board of Health and Welfare (64), reporting of all newly diagnosed tumours to the SCR is mandatory for clinicians, pathologists and cytologists as well as cases diagnosed at autopsy. This register includes information on selected demographic characteristics, tumour site, date of diagnosis, histological type and stage at diagnosis (collected since 2004). As a complement, there are about 25 national cancer quality registers that contain detailed information in demographic factors, clinical characteristics and aspects of management. Research based on quality registers can give some possible explanations of differences in cancer survival, treatment praxis etc in correlation to for example tumour stage or performance status on local, regional or national level.

The National Health Care Register in Sweden is also administrated by the National Board of Health and Welfare. Every county council reports specific data of consumption including diagnoses and treatment codes (KVÅ) every year to this national register. But there is more information in the register on the county council level than reported to the national. Since July 1th 2005 the Swedish National Prescribed Drug Register also is administrated by the National Board of Health and Welfare.

Register of costs in Sweden have been evaluated since 15-20 years both on local and national level. The national register is administrated by the Swedish Association of Local Authorities and Regions (SALAR) and every hospital in Sweden with a system able to calculate “cost per patient" reports every year data being more detailed for every year. The reporting hospitals are allowed to analyse all data in this national system. Via internet it is also possible for everyone to get non-identification data at an aggregate level from this system. The county council of Skåne has an own cost-database, often used for calculations on national level.

5.3 Survival analyses

Survival analysis is just another name for time to event analysis. The term survival analysis is used predominately in biomedical sciences where the interest is in observing time to death either of patients or of laboratory animals. When a subject does not have an event during the observation time, they are described as censored, meaning that we cannot observe what has happened to them subsequently. A censored subject may or may not have an event after the end of observation time (65, 66). Survival in cancer can be studied through analyses of overall survival, relative survival, recurrence free survival, or cancer specific survival. In the present thesis overall survival has been chosen as analytic tool knowing that overall survival analysis below age 60 highly correlate with cancer specific survival.

Population based register studies often include data for survival analyses with completeness and good quality. The validity of the available information is therefore often high and it is relatively easy to censor. Many different groups have interest in data of survival/mortality. The clinicians want to know the effects of different treatments and the politicians want to have information for decisions about allocation of resources. Finally, the patient wants to get the best practise and the general public wants the health care to be fair and equal.

There are several factors, such as comorbidity and the patient´s life style (including socioeconomic factors) that might distort the interpretation of survival differences between patients from various groups. For example, how does a given comorbidity lead to decreased survival? Does it affect stage at diagnosis, choice of treatment, compliance with the therapeutic regimen, treatment response, or perhaps all of these points in the patient's care? (43)

5.4 Cost analyses

Few studies have used a population-based approach and healthcare consumption, outcome and costs on an individual level have seldom been studied (14, 15). In a recent published article, "Cost efficiency of university hospitals in the Nordic countries: a cross-country analysis" (67) presents significant differences in university hospital cost efficiency when variables for teaching and research are entered into the analysis, both between and within the Nordic countries. The results of a second-stage analysis show that the most important explanatory variables are geographical location of the hospital and the share of discharges with a high case weight. However, a substantial amount of the variation in cost efficiency at the university hospital level remains unexplained.

Baker et al. (36) have already 1991 assigned costs associated with each cancer to three post diagnostic time periods: 1) initial treatment, during the first three months following diagnosis 2) maintenance care, between initial and terminal treatment; and 3) terminal treatment during the final six months prior to death. Recently Krahn et al has presented results showing that costs are highest around two events, the cancer diagnosis and cancer death (37).

Cost of Cancer in the Nordic countries is a recent SINTEF-study funded by the Nordic Cancer Union (10). The study provides estimates and comparison of costs of cancer in all of the Nordic countries. It covers costs of hospital treatment and prescription drugs, screening programs for breast and cervical cancer, and public expenditures related to sickness absenteeism and early retirement. According to the study, cancer-related treatment costs can be expected to increase by 28 per cent by 2025 due to increasing cancer prevalence in the future. This estimate does not take into account future changes in treatment costs due to innovations in technology, cancer therapy and organization of treatment and is therefore likely to be on the low side. The increase amounts to an annual growth of 1.3 per cent or 0.9 per cent per capita. The rising costs of cancer treatment raise important questions concerning how to address future challenges including the question of sustainable growth, efficient use of available resources, advances in cancer prevention and treatment, and the impact of financial mechanisms. The cross-country comparisons among Nordic countries point to some interesting differences and areas where potential gains can be made.

6 AIMS

The overall aim of this thesis was to study different aspect of health, health care and health care costs on a population based level for persons with cancer and their partners, and from an individual level to explore the impact of different factors as comorbidities, tumour stage, performance status, treatment etc in incidence and survival. The aim was also to provide methods and platforms for continuous follow-up of care initiatives and results in the total episode of care especially with extent of tumour diseases and comorbidities.

The more specific aims were:

- **Paper I:** Examine health care use and health care costs among partners of cancer patients with five common types of cancer before and after cancer diagnosis.

- **Paper II:** Investigate the role of dementia for 18 cancer diagnoses with the main question of a lower incidence of cancer in patients with dementia.

- **Paper III:** Examine and analyse all direct health care costs among patients with prostate cancer in the pre and post diagnostic phase of the disease. The aim was also to examine if outcomes of ill health in terms of health care use and health care costs increased among partners of prostate cancer patients.

- **Paper IV:** Study how the incidence of cancer for 18 cancer diagnoses is related to diabetes, obesity or abnormal blood lipids.

- **Paper V:** Examine and analyse all direct health care costs among patients with lung cancer and their partners in the pre and post diagnostic phase of the disease, especially treatment costs for patients. The aim was also to examine factors influencing survival in patients with non-small cell lung cancer (NSCLC).

7 MATERIAL AND METHODS

7.1 Design

The studies in this thesis were conducted using a population based cohort design. Individual information about patients from the Swedish Cancer Register (Cancer Register of Southern Sweden) was linked to additional data from other population based register by the unique ten-digit personal identification number, see Figure 7.1. Since 1958, every patient diagnosed with cancer has been reported to this register of cancer. Only patients with invasive tumours were included.

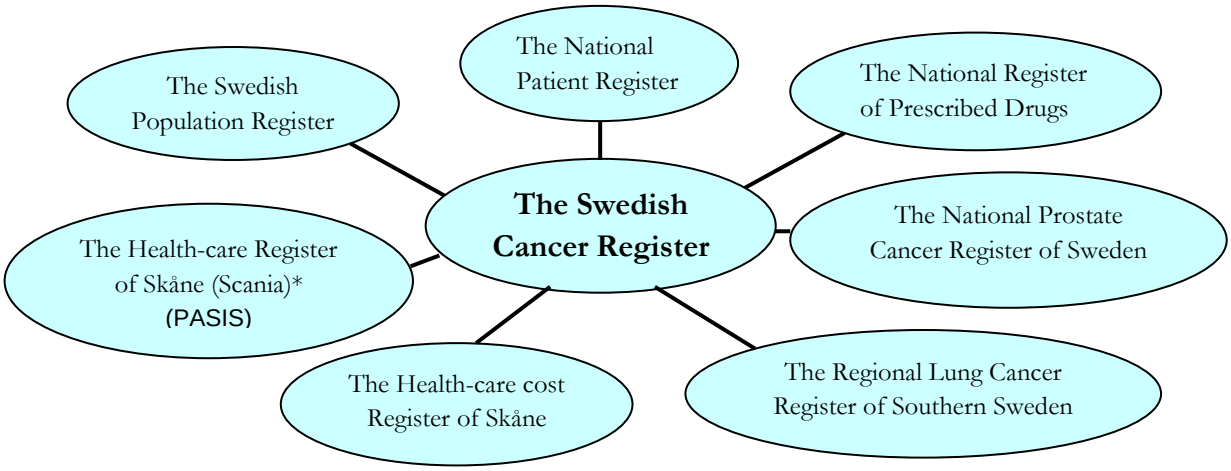

Figure 7.1. Schedule for data collection. * Public and private care

For each individual, patients as well as partners, health care consumption, health care costs and survival/mortality were monitored related to the patient´s date of diagnosis. Using this method the results could be calculated with time periods in days before and after diagnosis and proximity to death. When presenting the results, time periods are accumulated to years independent of the calendar year. Figure 7.2 illustrates these facts for both patients and partners.

The partner was defined as the adult spouse/partner living at the same address as the patient at the time of the cancer diagnosis. The partners were identified by the unique ten-digit personal identification number.

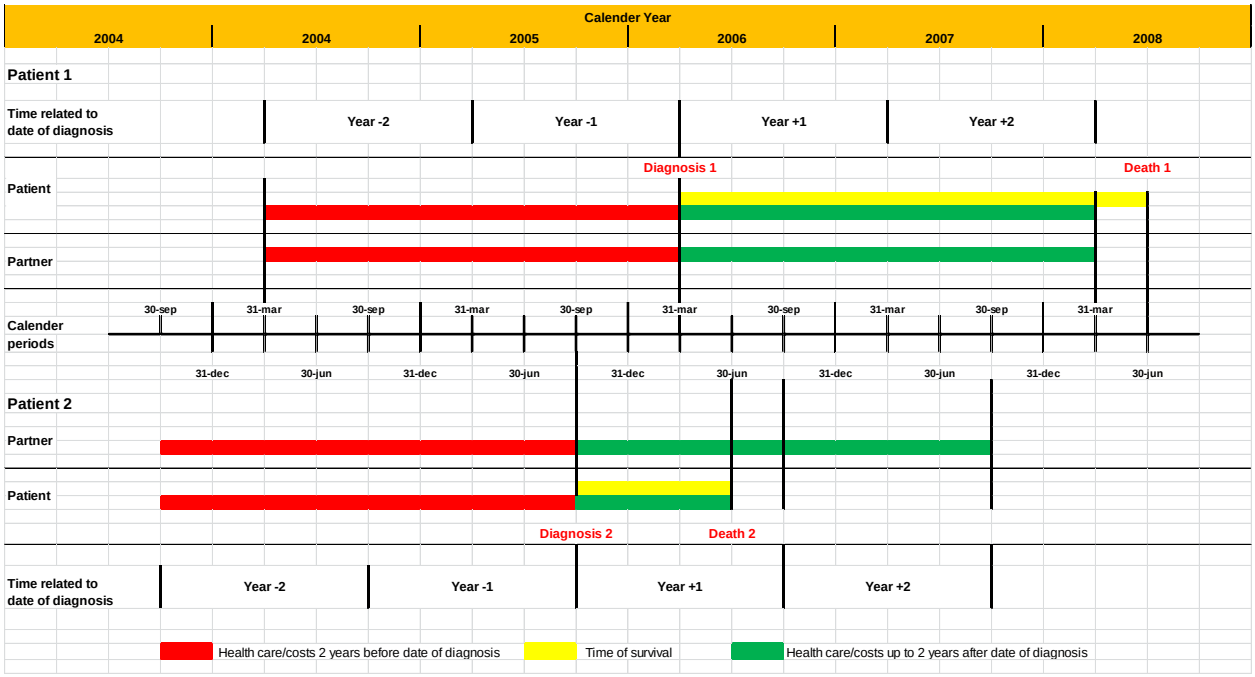

Figure 7.2. Time periods for different measures related to date of diagnosis

The design of the total study is shown in Figure 7.3. The investigations about sickness absence for patients and sick leave for partners (part II) are not presented in this thesis but are summarized in chapter "8.2 Additional reports and articles". In the thesis "Living with cancer – Impact on cancer patient and partner", Katarina Sjövall has described part II and part III.

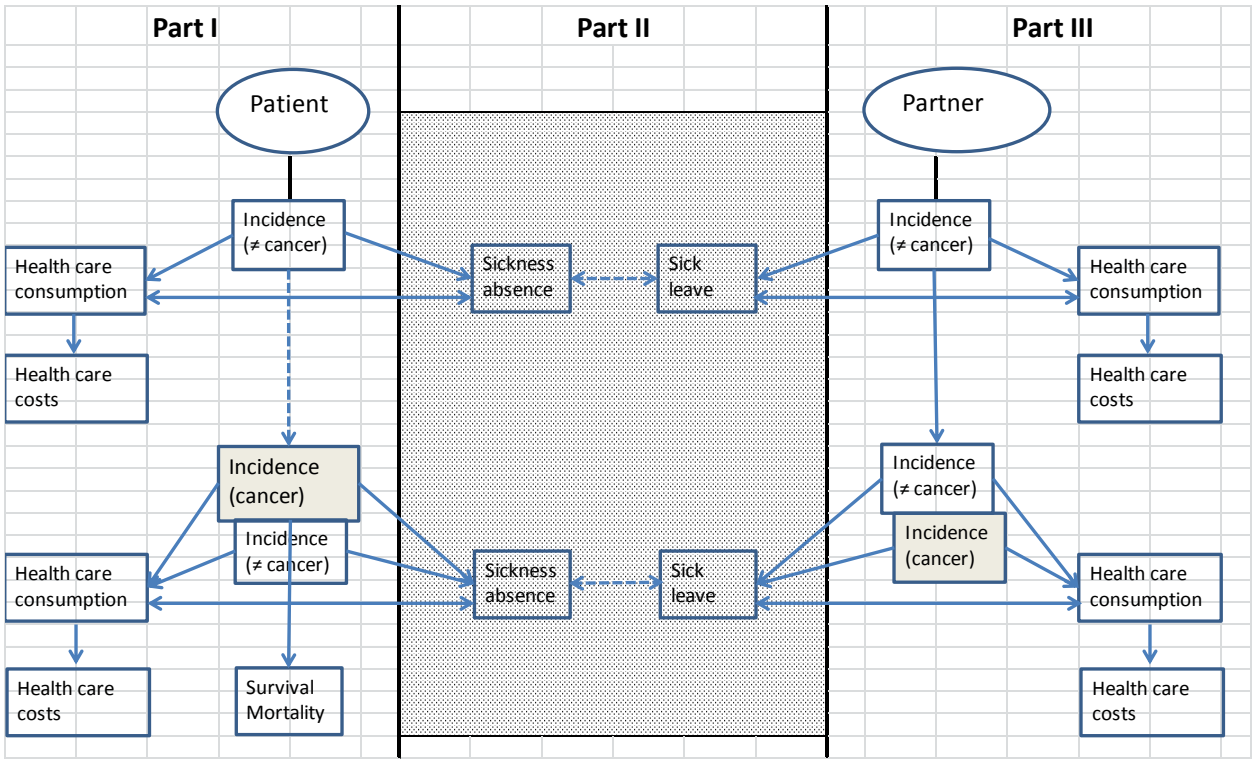

Figure 7.3. The design of the total study

An overview of the design in the different papers is presented in Table 7.1.

Table 7.1. Design of paper I-V

	Paper I	**Paper II**	**Paper III**	**Paper IV**	**Paper V**
Design	Longitudinal, retrospective cohort study	Longitudinal, retrospective cohort study	Longitudinal, retrospective cohort study	Longitudinal, retrospective cohort study	Longitudinal, retrospective cohort study
Domicile	Skåne (Scania)	Skåne (Scania)	Skåne (Scania)	Skåne (Scania)	Southern Health Care Region/ Skåne (Scania)
Data sources	Register data, see chapter 7.2.1	Register data, see chapter 7.2.1	Register data, see chapter 7.2.1	Register data, see chapter 7.2.1	Register data, see chapter 7.2.1
Subjects	**Partners** of persons with colon, rectal, breast, prostate and lung cancer	Persons with 18 types of cancer (**patients**)	Persons (**patients**) and **partners** of persons with prostate cancer	Persons with 18 types of cancer (**patients**)	Persons (**patients**) and **partners** of persons with lung cancer
Control persons/ reference subjects	General population, themselves	Up to eight controls per case matched for age (born in the same year), gender and domicile	General population, themselves (partners)	Up to eight controls per case matched for age (born in the same year), gender and domicile	General population, themselves (partners)
Study population/ control persons	See Table II	See Table II	See Table II	See Table II	See Table II
Time periods, incidence, diagnoses	2000-2005	2005-2007	2000-2005	2000-2007	2000-2005 A* 2002-2005 B* 2000-2007 C*
Time periods, comorbidity data		2004-2007		1998-2007	
Time frame	Two years before – two years after the cancer diagnosis	4 years before: 9-45 months	Two years before – two years after the cancer diagnosis	Ten years before: 90-1 460 days 90-3 650 days	A, C: Two years before – two years after the cancer diagnosis B: up to 4 years C: up to 8 years
Outcomes	Diagnosed diseases, morbidity, health care use, health care costs.	Diagnosed diseases, morbidity.	Diagnosed diseases, morbidity, health care use, health care costs.	Diagnosed diseases, morbidity.	Diagnosed diseases, morbidity, health care use, survival/ mortality, health care costs.
Data analysis	Descriptive statistics. Health care use: RR - 95% CI. Diagnosis: RR – 95 CI. Health care costs compared with general population (stand) and index.	Descriptive statistics. Comorbidity and cancer: RR - 95% CI, conditional logistic regression.	Descriptive statistics Total HC-costs compared general population (stand) and index.	Descriptive statistics. Comorbidity and cancer: RR - 95% CI, conditional logistic regression. In the multivariate analysis, each comorbidity factor was simultaneously adjusted for.	Descriptive statistics. Mortality for patients with NSCLC: RR – 95 CI, Cox proportional hazard model, each factor was simultaneously adjusted for.

* Different study populations, see chapter 7.2.2

7.2 Materials

7.2.1 Data sources

7.2.1.1 The Swedish Cancer Register

The Swedish Cancer Register (SCR), established in 1958, covers the total Swedish population and is administrated by the National Board of Health and Welfare. According to Regulations by the National Board of Health and Welfare (64), with the primary aim of monitoring cancer incidence and mortality trends, all physicians in hospitals and other establishments for medical treatment under public or private administration in Sweden must report all malignant and certain benign tumours to the Cancer Register. Furthermore, pathologists and cytologists separately report every tumour diagnosed from surgically removed tissues, biopsies, cytological specimens, bone marrow aspirates and autopsies. Thus, the majority of cases are notified twice, in separate reports. Only persons that have official residency in Sweden are included in the Cancer Register (39). Every health care region administrates its own registration of data and we therefore in some papers have called this part of the register the Cancer Register of Southern Sweden.

7.2.1.2 The Swedish Population Register

The Swedish Population Register is a national register containing vital statistics. This includes date of birth, gender, residential address, marital status, and the personal identification number on all Swedish residents. It was used to identify partners of the person with cancer, living at the same address at the date of the cancer diagnosis and also to check that both patients and control persons were living in Scania (Skåne) at a specific date in the studies. Every county administrates its part of the register and we therefore in papers have called the local register in Scania (Skåne) for the Population Register of Scania (Skåne).

7.2.1.3 Health care register; National and Skåne

Every county council report once a year specific data of all patients to the National Board of Health and Welfare which administrates The National Health Care Register, also called the National Patient Register. It includes since 1987 information on hospital admissions from all public hospitals in Sweden. Each inpatient discharge record contains for example dates of admissions and up to eight discharge diagnoses coded to IDC 10, codes of treatment/activities (KVÅ) and diagnosed related group (DRG). Since 2004 the county councils also report visits to doctors.

In the study we also have used the Health Care Register of Skåne, also called PASiS, a county council administration system which contains more information than reported to the National Board of Health and Welfare. It covers all consumption of publicly organised health care in Skåne, except for school and industrial health service. The system contains individually based data on inpatient and outpatient health care and includes for example visits to doctors since about 1970.

7.2.1.4 Register of Health Care Cost in Skåne

In the county council of Skåne the administration combines the records from the Health Care Register of Skåne with data from a patient cost data base by the unique individually personal identity number creating the Health Care Cost Register of Skåne.

In the register costs are obtained for each individual for all (not only for patients in Skåne) in- and outpatient contacts. University hospitals in Skåne use advanced models with Activity-Based Costing (ABC) methodology for all the different health-care services provided to individual patients. The costs per patient for health-care in other hospitals in Region Skåne are calculated by matching each

hospital own cost per Diagnosis-Related Group (DRG) per clinic to the individual patient by the patient´s classified DRG. For primary care the register use the average cost per visit to each clinic.

7.2.1.5 The Swedish Prescribed Drug Register

Since July 1st 2005 the National Board of Health and Welfare administrates the Swedish Prescribed Drug Register. The register contains information about all prescribed pharmaceuticals.

7.2.1.6 The Regional Prostate Cancer Register in Southern Sweden

The Prostate Cancer Register is a regional (the Regional Prostate Cancer Register in Southern Sweden) as well as a national register (the National Prostate Cancer Register of Sweden) used for quality follow-ups and quality improvements of the prostate cancer care. It contains information on mode of detection, TNM stage, Gleason score, serum levels of prostate specific antigen (PSA) and primary treatment within six months of date of diagnosis.

7.2.1.7 The Regional Lung Cancer Register in Southern Sweden

The Regional Lung Cancer Register in Southern Sweden is population based and was established in 1995 to monitor quality of care after the introduction of regional management guidelines for lung cancer. The register contains detailed information on gender, age at diagnosis, waiting time, smoking status (current, former and non-smoker), performance status (according to the WHO classification), mode of detection, diagnostic procedures, histopathology, stage at diagnosis (according to the TNM classification) and planned initial treatment (surgery, chemotherapy, radiotherapy and no active curative treatment).

7.2.2 Study populations

In paper I, persons diagnosed with colon, rectal, breast, prostate and lung cancer during the period 2000-2005 and living in Skåne were identified via the Cancer Register of Southern Sweden (see Table 7.2). The same study population for patients and partners was used in paper III and paper V.

Table 7.2. Description sample of partners to cancer patients diagnosed 2000-2005, study populations for partners in paper I (all five types of cancer), and for patients and partners in paper III (prostate cancer) and paper V (lung cancer, part A).

	No. of patients	**No. of partners**	**Age of partner >65 years**	**Gender of partner**
Diagnosis of patient	**N**	**N (%)**	**% of total sample**	**Male / Female**
Colon cancer	2976	1440 (48)	68 %	38 % / 62 %
Rectal cancer	1455	729 (50)	58 %	36 % / 64 %
Lung cancer	2920	1488 (51)	58 %	35 % / 65 %
Breast cancer	5318	2559 (48)	38 %	99 % / 1 %
Prostate cancer	7319	4860 (66)	54 %	0.1% / 99.9%
Total	19 988	11 076 (55)	53 %	35 % / 65 %

In paper V we have three different study populations (A-C). Part A is presented in Table 7.2 above. The two other populations, parts B-C are presented in Table 7.3-7.4.

Table 7.3. Number of cases of lung cancer stratified by stage, gender and age-group 2002-2005 in the county of Skåne, study population in paper V, part B.

Gender	**Age-group**	**Stage**								
		Not registered	**IA**	**IB**	**IIA**	**IIB**	**IIIA**	**IIIB**	**IV**	**Total**
Female	0-69	10	71	39	2	8	42	92	218	482
	70-	3	47	47		18	34	73	159	381
	Total	13	118	86	2	26	76	165	377	863
Male	0-69	10	44	58	3	14	28	125	230	512
	70-	16	45	68		23	34	118	211	515
	Total	26	89	126	3	37	62	243	441	1 027
Total		39	207	212	5	63	138	408	818	1 890

Table 7.4. Number of cases of lung cancer stratified by diagnosis and geographic area 2000-2007 in the Southern Health Care Region, study population in paper V, part C.

		Geographic Area								
Diagnosis group	**Diagnosis**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Total**
Small cell lung cancer		102	59	127	92	27	43	38	55	543
Non-small cell lung cancer	Adenocarcinomas	144	185	253	183	63	85	85	118	1 116
(NSCLC)	Large cell carcinomas,	74	50	254	165	37	100	31	54	765
	Squamous cell carcinomas	128	89	194	150	32	50	66	41	750
	Carcinoid	17	4	16	13	6	9	0	8	73
	Others	32	32	41	72	17	11	12	20	237
Total NSCLC		395	360	758	583	155	255	194	241	2 941
Not registered				1		1		1		3
Total		497	419	886	675	183	298	233	296	3 487
Total NSCLC except carcinoid		378	356	742	570	149	246	194	233	2 868
Total NSCLC except carcinoid and except missing in mortality analysis										2 726

An overview of the study populations for patients in paper II and paper IV is presented in Table 7.5. All patients with cancer diagnoses from 2005–2007 were identified in the Cancer Register for Southern Sweden. Only patients who were identified in the Population Register of Scania 2003-12-31 were included. In total, the study covers 19,756 cases of cancer. Eight controls per case matched for age (born in the same year), gender and domicile (in some cases fewer controls due to the inclusion criteria) were identified in the Population Register for Scania on the same day as the cases, 2003-12-31. After checking in the Cancer Register for Southern Sweden that the control persons had no prior diagnosis of cancer and in the Population Register for Scania that they were alive at the time of the matched case was diagnosed, the total cohort consisted of 19,756 cases and 147,324 controls, totally 167,080 individuals.

The comorbidity diagnoses of dementia in paper II (ICD 10: F00-03, G30,) and diabetes, obesity and abnormal blood lipids in paper IV (see Table I) were identified from the Health Care Registries in Scania (outpatient and inpatient), from 2004 to 2007 for both cases and controls with the same risk time calculated for the control as the matched case in a time period of 0-4 years depending on the date of diagnosis of the cancer patient. In paper IV we also identified the comorbidity diagnoses for the period 1998 to 2003; totally 1998 to 2007, a time period of 0-10 years. In the analysis, we excluded the 90 days immediately prior to the date of the cancer diagnosis. The follow-up time in paper IV was divided in two periods, 0–4 years and more than 4 years. The health care registries in Scania cover the total consumption of publicly organized inpatient and outpatient care, but in primary care, contacts are registered without diagnoses before 2004. Therefore, in the paper IV we first present data for the 4 years of follow-up and then extend the analysis to include the 10 years of follow-up. For the extended comorbidity study, we also required both patients and controls to be residents in the county 1997-12-31; leaving 19,058 cases and 141,333 controls.

Table 7.5. Study populations for patients and controls in paper II and paper IV.

			Paper II			Paper IV		
Type of cancer			Cases	Controls	Total	Cases	Controls	Total
ICD 10	Name	Analysis[a]	(n)	(n)	(n)	(n)	(n)	(n)
C16	Gastric cancer	A	387	2 836	3 223	387	2 836	3 223
		B				380	2 737	3 117
C18-C19	Colon cancer	A	1 603	11 761	13 364	1 603	11 761	13 364
		B				1 557	11 364	12 921
C20-C21	Rectal cancer	A	791	5 881	6 672	791	5 881	6 672
		B				769	5 683	6 452
C22-C24	Liver cancer	A	283	2 093	2 376	283	2 093	2 376
		B				270	2 018	2 288
C25	Pancreatic cancer	A	316	2 365	2 681	316	2 365	2 681
		B				304	2 272	2 576
C34	Lung cancer	A	1 623	12 301	13 924	1 623	12 301	13 924
		B				1 567	11 842	13 409
C43	Melanoma	A	955	7 150	8 105	955	7 150	8 105
		B				924	6 781	7 705
C44	Other skin cancer	A	1 546	10 591	12 137	1 546	10 591	12 137
		B				1 509	10 321	11 830
C50	Breast cancer	A	2 724	20 842	23 566	2 724	20 842	23 566
		B				2 613	19 898	22 511
C53	Cervical cancer	A	178	1 370	1 548	178	1 370	1 548
		B				163	1 251	1 414
C54	Endometrial cancer	A	471	3 569	4 040	471	3 569	4 040
		B				460	3 452	3 912
C56	Ovarian cancer	A	289	2 207	2 496	289	2 207	2 496
		B				280	2 111	2 391
C61	Prostate cancer	A	3 545	26 654	30 199	3 545	26 654	30 199
		B				3 424	25 707	29 131
C64	Kidney cancer	A	379	2 888	3 267	379	2 888	3 267
		B				362	2 766	3 128
C66-C68	Urinary tract/ bladder cancer	A	1 123	8 278	9 401	1 123	8 278	9 401
		B				1 093	8 043	9 136
C71	Brain tumours	A	214	1 663	1 877	214	1 663	1 877
		B				196	1 531	1 727
C82-C85	Lymphoma	A	425	3 176	3 601	425	3 176	3 601
		B				415	3 017	3 432
C91-C95	Leukemia	A	340	2 527	2 867	340	2 527	2 867
		B				317	2 335	2 652
C00-C96, D45	Others	A	2 564	19 172	21 736	2 564	19 172	21 736
		B				2 455	18 204	20 659
	Total	A	19 756	147 324	167 080	19 756	147 324	167 080
		B				19 058	141 333	160 391

A=Uni, 0-4 year; B=Multi, 0-10 year

7.2.3 Comorbidity data

In the second and third report from SRHCC, based on data for five types of cancer, some results were presented about the correlation between comorbidity and cancer for patients in the most common types of cancer. The information from these early investigations was complemented with data about partners comorbidities used in paper I describing the different diseases partners had before and after the patient´s diagnosis of cancer.

In the later part of the study the investigations focused on the correlation between 18 specified types of cancer and some different diseases/groups of diseases, see Table 7.6:

Table 7.6. Diseases in investigation of correlation with cancer.

ICD 10	Name
B 15-B19	Hepatises
D50-D64	Anaemias
E10-E14	Diabetes
E66	Obesity
E78	Abnormal blood lipids
E244	Alcoholic related diagnoses
F00-F03,G30	Dementia and Alzheimer's disease
F32-F33	Depressive episodes
H90	Conductive and sensorineural hearing loss
I10-I13, I15	Hypertensive diseases
I10-I25	Ischemic Heart diseases
I60-I69	Hemorrhages
J43-J44	Chronic Obstructive Pulmonary Disease
K50-K51	Crohn's disease/ulcerative colitis
M05-M06	Rheumatoid arthritis
N60-N64	Diseases/disorders of breast
Z80-Z84	Family history

In two papers we have described the correlations in incidence between comorbidity and cancer; dementia and cancer (paper II) and diabetes, obesity, abnormal blood lipids and cancer (paper IV).

The information about other diseases was also used in paper V when analysing factors influencing survival in patients with non-small cell lung cancer (NSCLC).

7.3 Statistical analysis

7.3.1 Paper I

Health care use, diagnosis and total costs of health care were studied for continuous periods of one year pre-diagnose and one year post-diagnose, and for two years pre- and post-diagnose.

Diagnoses of the partner were compared for the periods before and after the cancer patient´s diagnosis and analysed for the whole period. In order to analyse and compare the period pre diagnosis with post diagnosis, relative risk (RR) was computed. RR was computed with 95% confidence intervals (CI) for a ratio of two independent proportions, large sample.

Health care use (defined by in- and outpatient care and days in hospital) was compared for one and two years after to the one year before the cancer diagnosis. RR was computed with 95% CI. The comparison one year post diagnosis was based on the population diagnosed 2001-2005, and the comparison two years post diagnosis was based on the population diagnosed 2001-2004.

Total costs of health care of partners were compared with total costs for the general population standardized for age, gender and marital status during the same period of time. Mean health care costs per month and partner were calculated for the period of 24 months pre diagnosis until 24 months post diagnosis, and was compared with consumers prize index for the same period of time.

7.3.2 Paper II

All patients with cancer diagnoses from 2005–2007 were identified in the Cancer Register for Southern Sweden. The comorbidity diagnoses of dementia (ICD 10: F00-03, G30, see table V) were identified from the Health Care Registries in Scania (outpatient and inpatient), from 2004 to 2007 for both cases and controls with the same risk time calculated for the control as the matched case in a time period of 9–45 months depending on the date of diagnosis of the cancer patient (we excluded the nearest 90 days prior the date of cancer diagnosis). Risk ratios (RR) with 95% confidence intervals (CI) were calculated using conditional logistic regression, Stata for Macintosh, 10.0. The models were stratified for age and gender.

7.3.3 Paper III

All persons diagnosed in Skåne with prostate cancer in the period 2000 to 2005 were identified via the Cancer Register of Southern Sweden. Data on Gleason score, and treatment types were obtained from the Prostate Cancer Register. Partners to the prostate cancer patients were identified via Population Register of Sweden when living at the same address at the time of the patient´s cancer diagnosis. Comparisons of health care costs for the whole study period were made with the standard population in the Southern Health Care Region matched for age and gender and with breast cancer patients in Region Skåne.

Partners' health care costs were obtained in the same way as described above with in- and outpatients' costs. They were monitored related to the date of diagnosis of the prostate cancer patient. Health care costs were compared to those of the general population, matched for age, gender and marital status.

7.3.4 Paper IV

All patients with cancer diagnoses from 2005–2007 were identified in the Cancer Register for Southern Sweden.

The comorbidity diagnoses of diabetes (ICD 10: E10-14), obesity (ICD 10: E66) and blood lipid abnormality (ICD 10: E78) were identified from the Health Care Registries for Scania (outpatient and inpatient), 1998–2007, for both cases and controls with the same risk time calculated for the control as for the matched case, in a time period of 0–10 years, depending on the diagnosis date for the cancer patient. For the extended comorbidity study, we also required both patients and controls to be residents in the county 1997-12-31; leaving 19,058 cases and 141,333 controls. In the analysis, we excluded the 90 days immediately prior to the date of the cancer diagnosis. The follow-up time was divided in two periods, 0–4 years and more than 4 years. These registries cover the total consumption of publicly organized inpatient and outpatient care, but in primary care, contacts are registered without diagnoses before 2004. Therefore, in the manuscript we first present data for the 4 years of follow-up and then extend the analysis to include the 10 years of follow-up.

Risk ratios (RR) and 95 % confidence intervals (CI) for a diagnosis of diabetes, obesity or blood lipids abnormality prior to cancer diagnosis for the case in relation to type of cancer, were calculated using conditional logistic regression (CLR), Stata for Macintosh, 10.0. The univariate models were stratified for age and gender, and in the multivariate analysis, each comorbidity factor (diabetes, obesity and abnormal blood lipids) was simultaneously adjusted for.

7.3.5 Paper V

All persons diagnosed with lung cancer in the period 2000 to 2007 were identified via the Cancer Register of Southern Sweden. Data on tumour stage and treatment types were obtained from the Lung Cancer Register. Partners to the lung cancer patients were identified via Population Register of Sweden when living at the same address at the time of the patient´s cancer diagnosis. Comparisons of health care costs for the whole study period were made with the standard population in the Southern Health Care Region matched for age and gender

Partners' health care costs were obtained in the same way as described above with in- and outpatients' costs. They were monitored related to the date of diagnosis of the prostate cancer patient. Health care costs were compared to those of the general population, matched for age, gender and marital status.

To analyse factors influencing survival/mortality risk ratios (RR) and 95 % confidence intervals (CI) for patients with NCSLC for the case in relation to all factors were calculated using Cox proportional hazard model, SPSS for Macintosh, version 19. In the multivariate analysis, each factor was simultaneously adjusted for. Variables included in the statistical model were: age, gender, tumour stage, performance status (WHO), smoker, alcoholic related disease, diabetes (ICD 10: E18), anaemias (ICD 10: D50-D64), rheumatoid arthritis (ICD 10: M05-M06), chronic obstructive pulmonary disease (ICD 10: J43-J44), hypertensive diseases (ICD 10: I10-I15), no treatment, chemotherapy (primary), radiotherapy (primary), surgery (primary), short waiting time (time between date of diagnosis and date of decision about treatment ≤ 21 days), adenocarcinomas, large cell carcinomas, squamous cell carcinomas and living in geographic area A-H.

8 SUMMARY OF STUDIES

8.1 Original articles/papers in the thesis

8.1.1 Study I: Influence on the health of the partner affected by tumour disease in the wife or husband based on a population-based register study of cancer in Sweden

Introduction
A cancer disease not only has direct consequences for the patient with cancer but can also affect the life of the partner and the family. The partner is often the closest relative to the cancer patient and has an important role in providing support. The findings from the literature review may imply that partners of persons with cancer disease have an increased use of health care but no previous population-based studies have been found with the focus on health care use in partners of persons with cancer. The purpose of this study was to examine health care use and health care costs among partners of persons with cancer.

Material and Methods
The study cohort consisted of partners of patients diagnosed with colon, rectal, lung, breast, and prostate cancer (N =11,076) in the years 2000 to 2005 in the region of Skåne. Partner was defined as the adult/spouse living with at the same address as the patient at the time of the cancer diagnosis according to the Swedish Population Register. Data were collected from the Swedish Cancer Register (Tumour Register of Southern Sweden) and linked to the Swedish Population Register (Census Registry of care Sweden) and to Health care registries of Southern Sweden.

Health care use (in- and outpatient care and days in hospital) was compared for 1 and 2 years after with 1 year before the cancer diagnosis and risk ratio (RR) was computed with 95% CI. In order to analyse and compare the pre diagnosis and post diagnosis periods, RR was computed; the group of partners was compared with themselves before and after the cancer diagnosis. RR was computed with 95% CI for a ratio of two independent proportions, large sample. The comparison 1 year post diagnosis was based on the population diagnosed 2001 to 2005, and the comparison 2 years post diagnosis was based on the population diagnosed 2001to 2004.

Diagnosis of the partner was compared before and after diagnosis of the patient and analysed for the whole period. In order to analyse and compare the period pre diagnosis with post diagnosis, RR was computed with 95% CI for a ratio of two independent proportions, large sample. Total costs of health care per partner were compared with total costs for the general population standardized for age, sex, and marital status during the same period of time. Mean health care costs per month and partner were calculated for the period of 24 months pre diagnosis until 24 months post diagnosis, and was compared with consumers prize index for the same period of time. Costs are presented in Swedish crowns (SEK), (1 US dollar is equal to approximately 8 SEK).

Results
Health care use for partners increased in terms of in-patient care after the cancer diagnosis. The increase was significant for partners of patients with colon cancer the first year after the cancer diagnosis RR=1.43 (95% CI, 1.21 to 1.68). A significant increase was also seen the second year for partners of patients with colon cancer RR=1.55 (95% CI, 1.28 to 1.87) and lung cancer RR=1.50 (95% CI, 1.26 to 1.79). Diagnosis in total among partners increased the year after the cancer diagnosis. The largest increase was seen for psychiatric diagnoses. The increase was significant for the total sample RR=2.02 (95% CI, 1.73 to 2.37), with significant increases for partners of colon

(RR, 2.66; 95% CI, 1.71 to 4.22), lung (RR, 3.16; 95% CI, 2.23 to 4.57), and prostate cancer patients (RR, 1.68; 95% CI, 1.32 to 2.15).

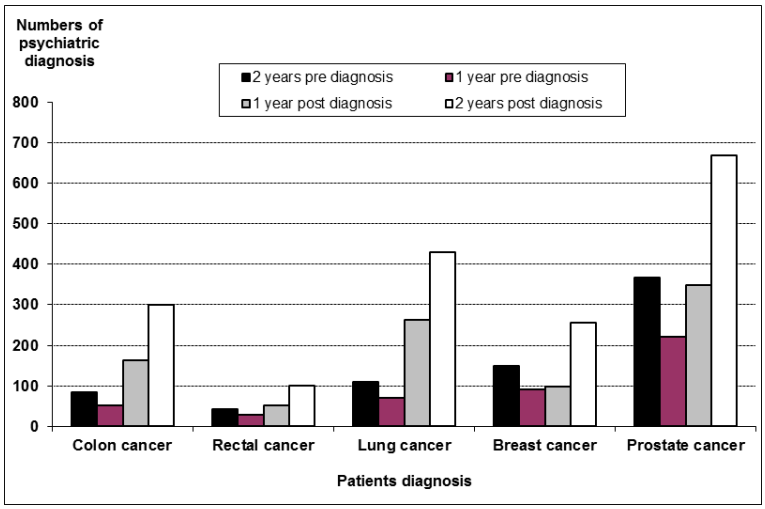

Figure 8.1. Number of psychiatric diagnoses for partners 1-2 years pre diagnosis and 1-2 years post diagnosis

Health care costs increased the first and the second year after the cancer diagnosis in all five diagnosis groups (Fig 8.1). When comparing with consumers prize index, the increase was higher from the time of the diagnosis and for the two following years (Fig 8.2). In comparison to the general population standardized for age, sex and marital status, male partners had a higher increase than female partners. Health care costs for partners were in general lower than health care costs for the standardized population. Younger male partners (25 to 64 years) had a larger increase compared to the general population.

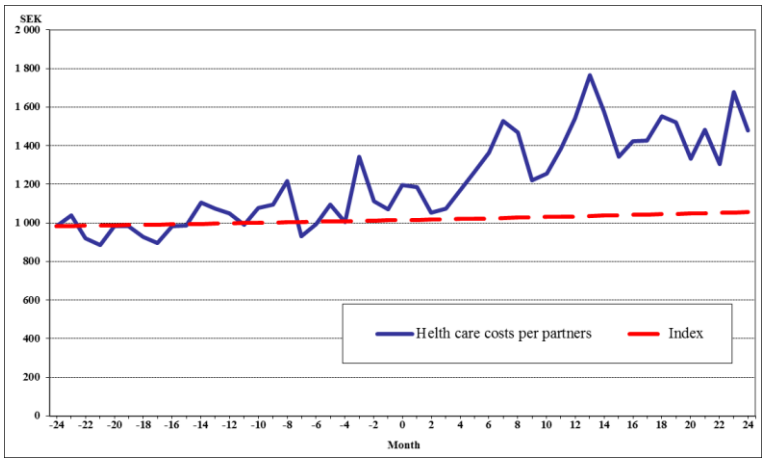

Figure 8.2. Health care costs (mean) per partners and month during a period or 4 years in all types of cancer.

Conclusion

In conclusion, patients' type of cancer and disease stage has an impact on partners' reaction and its consequences in terms of health care use and health care costs. Being a partner of a person with cancer means an increased risk in psychiatric morbidity. With an increase in cancer incidence, treatments with longer duration and a major part of cancer care are provided on an outpatient basis, which means that the demands and burden on the family of the cancer patient are likely to increase. Discussion is needed about the responsibility for the care of the partner—should oncology care also include the family? The emotional and physical well-being of the partner is of importance both from a medical point of view as well as of social perspective. Future studies are also planned to investigate sick leave for the partner, in order to further explore the indirect costs of cancer related to the partner.

8.1.2 Study II: Low cancer rates among patients with dementia in a population–based register study in Sweden

Background
Studies on the influence of comorbidity on incidence and survival of cancer have generally focussed on one cancer form and on one comorbidity at a time and often been in the form of cross-sectional and case-control studies. In register-based studies often only inpatient data have been used, leading to an underestimation of the comorbidity itself. Chronic diseases that have been reported to show a lower risk of cancer include dementia. In this population-based register study we used both out- and inpatient data and investigated the role of dementia for 18 cancer diagnoses with the main question of a lower incidence of cancer in patients with dementia.

Material and Methods
All patients with cancer diagnoses from 2005 to 2007 were identified in the Cancer Register of Southern Sweden. Every patient with diagnosed cancer is reported to this register since 1958. Only patients who were identified in the Population Register of Scania 2003-12-31 were included. Totally the study covers 19,756 cases of cancer (gastric, colon, rectal, liver, pancreatic, lung, melanoma, skin cancer, breast, cervical, endometrial, ovarian, prostate, kidney, brain, lymphoma and leukaemia). Only patients with invasive tumours were included.

Age- and gender-matched controls, 8 controls per case (in some cases fewer controls due to the inclusion criteria) were identified in the Population Register of Scania at the same date as the cases, 2003-12-31. After checking in the Cancer Register of Southern Sweden that control persons had no prior diagnosis of cancer and in the Population Register of Scania that they were alive at the time of diagnosis of the matched case, 147,324 controls remained. The comorbidity diagnoses of dementia (ICD 10: F00-03, G30, were identified from the Health Care Registries in Scania (outpatient and inpatient), from 2004 to 2007 for both cases and controls with the same risk time calculated for the control as the matched case in a time period of 9–45 months depending on the date of diagnosis of the cancer patient (we excluded the nearest 90 days prior the date of cancer diagnosis). These registries cover all consumption of publicly organized in- and outpatient care. Risk ratios (RR) with 95% confidence intervals (CI) were calculated using conditional logistic regression, Stata for Macintosh, 10.0. The models were stratified for age and gender.

Results
Overall a diagnosis of dementia was significantly less common among the cancer cases (RR = 0.60, 95% CI = 0.52–0.69). The reduced risk was more pronounced for patients older than 70 years than for patients younger than 70 years (RR = 0.59, 95% CI = 0.52–0.68, vs. RR = 0.73, 95% CI = 0.45–1.19). A significantly lower risk of dementia was seen in patients with colon cancer (RR = 0.60, 95% CI = 0.40–0.91), lung cancer (RR = 0.53, 95% CI = 0.31–0.90), melanoma (RR = 0.44, 95% CI = 0.20–0.97), prostate carcinoma (RR = 0.49, 95% CI = 0.33–0.72) or urinary bladder/tract cancer (RR = 0.40, 95% CI = 0.22–0.73), and no diagnosis of dementia was found among patients with cervical cancer, brain tumours and leukaemia (table 2). Non significantly low risks were seen for all other studied tumour types. The low risks were most pronounced for tumours developing within the body compared to those presenting closer to the body surface. .

Conclusion
The study confirms previous findings that patients with dementia have a lower risk of cancer. Because the effect was seen for all tumour types and especially for patients older than 70 years and since the deficit was more pronounced for patients with tumours situated within the body, the data suggest that malignancies are underdiagnosed for persons with dementia.

8.1.3 Study III: Prostate cancer in the pre and post diagnosis phase – a population based study on health care costs

Introduction
Previous studies have shown that the cost burden of prostate cancer is high and varies according to treatment type. To date, limited information exists regarding health care costs for prostate cancer patients in the pre-diagnostic phase of the disease. Knowledge about costs in the last year of life for prostate cancer patients is also sparse; as such studies usually are conducted at an institutional level. Another perspective of prostate cancer related costs not yet fully investigated are the costs for the influence on relatives, for example the partner.

The aim of this study was to examine and analyse all direct health care costs among prostate cancer in the pre- and post-diagnostic phase of the disease. The aim was also to examine if outcomes of ill health in terms of health care use and health care costs increased among partners of prostate cancer patients.

Methods
We used population-based data for monitoring health care costs, including in- and outpatient care and pharmaceuticals. All persons diagnosed in Skåne with prostate cancer in the period 2000 to 2005 were identified via the Cancer Register of Southern Sweden. Data on Gleason score, and treatment types were obtained from the Prostate Cancer Register. Partners to the prostate cancer patients were identified via Population Register of Sweden when living at the same address at the time of the patient´s cancer diagnosis. Comparisons of health care costs for the whole study period were made with the standard population in the Southern Health Care Region matched for age and gender and with breast cancer patients in Region Skåne. Partners' health care costs were obtained in the same way as described above with in- and outpatients' costs. They were monitored related to the date of diagnosis of the prostate cancer patient. Health care costs were compared to those of the general population, matched for age, gender and marital status. Health care costs were monitored in relation to time periods before and after the prostate cancer diagnosis for both patients and their partners.

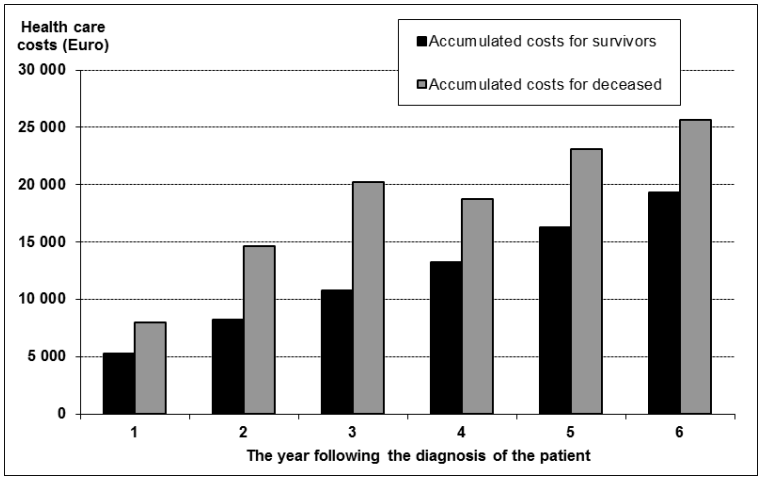

Figure 8.3: Accumulated health care costs (per patient) for prostate cancer patients, survivors and deceased

Results

The major part of health care costs for prostate cancer patients occurred during the first year following the diagnosis. A clear difference was seen between costs for survivors and costs for deceased; the first year following the diagnosis costs were about 50% higher for deceased and 2-3 times higher the following years, see Figure 8.3. Health care costs increased with higher Gleason score in the year following the diagnosis, see Figure 8.4. Higher health care costs were seen for patients treated with primary radiotherapy. Lowest costs were seen for patients with expectancy. Health care costs were higher for patients with curative treatments compared to those with palliative treatments.

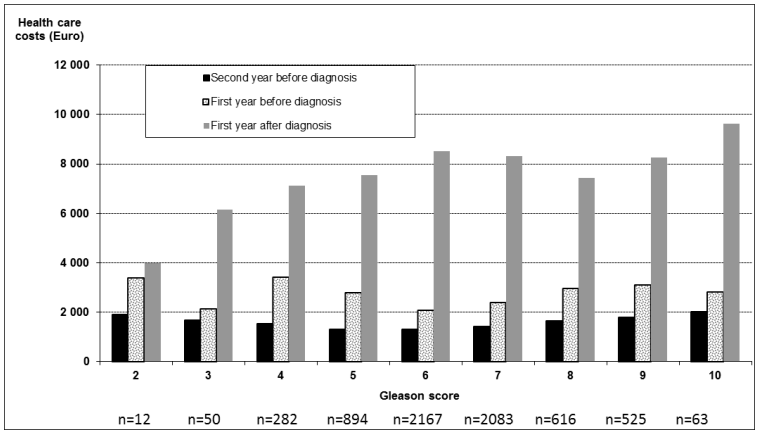

Figure 8.4: Health care costs per person and year for prostate cancer patients stratified by Gleason score.

When comparing health care costs for prostate cancer patients with those for breast cancer patients, costs per breast cancer patient were 50% higher during the first year post diagnosis. The following years post diagnosis costs were essentially the same (Figure 8.5).

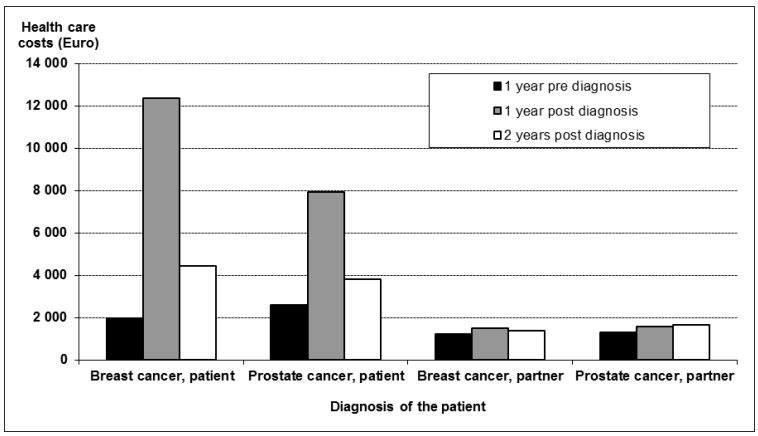

Figure 8.5: Comparison of health care costs (per person) prostate cancer versus breast cancer, patients and partners.

Partners had an increase in health care use both the first and second year following the diagnosis of the prostate cancer patient leading to an increase in health care costs. The cost burden of prostate cancer varies along the different phases of the disease.

Conclusions

Prostate cancer is an important issue in terms of health care decisions. In this study we have elucidated different perspectives of significance when calculating costs for prostate cancer. In future research this also needs to be considered, as costs of prostate cancer are likely to increase. When planning for care and allocation of resources for care the impact on the partner should also be considered.

8.1.4 Study IV: Cancer among patients with diabetes, obesity and abnormal blood lipids - a population-based register study in Sweden

Introduction

Studies of the influence of comorbidity on the incidence and survival rates for cancer have often focussed on one cancer form and on one comorbidity at a time and have mostly been in form of cross-sectional and case–control studies. Register-based studies have often used only inpatient data leading to an underestimation of the comorbidity itself. Chronic diseases that have been reported to be linked with a higher risk of cancer include diabetes and obesity. In this population-based register study, we used both outpatient and inpatient data and investigated the role of diabetes, obesity and hyperlipidaemia in 18 cancer diagnoses. We chose these three disease groups as they are partly interrelated and have recently received public attention in connection with prevention.

Methods

All patients with cancer diagnoses from 2005–2007 were identified in the Cancer Register for Southern Sweden. Only patients who were identified in the Population Register for Scania 2003-12-31 were included. In total, the study covers 19,756 cases of cancer (gastric, colon, rectal, liver, pancreatic, lung, melanoma, skin cancer, breast, cervical, endometrial, ovarian, prostate, kidney, urinary tract/ bladder, brain, lymphoma and leukaemia). Only patients with invasive tumours were included. Eight controls per case matched for age (born in the same year), gender and domicile (in some cases fewer controls due to the inclusion criteria) were identified in the Population Register for Scania on the same day as the cases, 2003-12-31. After checking in the Cancer Register for Southern Sweden that the control persons had no prior diagnosis of cancer and in the Population Register for Scania that they were alive at the time of the matched case was diagnosed, the total cohort consisted of 19,756 cases and 147,324 controls, totally 167,080 individuals.

The comorbidity diagnoses of diabetes (ICD 10: E10-14), obesity (ICD 10: E66) and blood lipid abnormality (ICD 10: E78) were identified from the Health Care Registries for Scania (outpatient and inpatient), 1998–2007, for both cases and controls, with the same risk time calculated for the control as for the matched case, in a time period of 0–10 years, depending on the diagnosis date for the cancer patient. For the extended comorbidity study, we also required both patients and controls to be residents in the county 1997-12-31; leaving 19,058 cases and 141,333 controls. In the analysis, we excluded the 90 days immediately prior to the date of the cancer diagnosis. The follow-up time was divided in two periods, 0–4 years and more than 4 years. These registries cover the total consumption of publicly organized inpatient and outpatient care, but in primary care, contacts are registered without diagnoses before 2004. Therefore, in the manuscript we first present data for the 4 years of follow-up and then extend the analysis to include the 10 years of follow-up.

Risk ratios (RR) and 95 % confidence intervals (CI) for a diagnosis of diabetes, obesity or blood lipids abnormality prior to cancer diagnosis for the case in relation to type of cancer, were calculated using conditional logistic regression (CLR), Stata for Macintosh, 10.0. The univariate models were stratified for age and gender, and in the multivariate analysis, each comorbidity factor (diabetes, obesity and abnormal blood lipids) was simultaneously adjusted for.

Results

Overall a diagnosis of diabetes was significantly more common among the cancer cases than the controls (RR = 1.14, 95 % CI = 1.09–1.21). Diabetes was more common prior to diagnosis in patients with liver cancer (RR = 3.43, 95 %CI = 2.49–4.74), pancreatic cancer (RR = 2.36, 95 % CI = 1.68–3.32), colon cancer (RR = 1.49, 95 % CI = 1.27–1.76), urinary tract/bladder cancer (RR = 1.21, 95 % CI = 0.99–1.48) and breast cancer (RR = 1.18, 95 % CI = 0.99–1.40). A significantly lower risk of diabetes was seen in patients with prostate carcinoma (RR = 0.81, 95 % CI = 0.72–0.93). This effect was stronger for patients under 65 years of age (RR = 0.66, 95 % CI = 0.50–0.87). Both males and females showed significantly increased risks of diabetes and liver cancer, pancreatic

cancer and colon cancer and the effect was greater in younger patients. Overall a diagnosis of obesity was not significantly more common in cancer cases vs controls (RR = 1.09, 95 % CI = 0.95–1.27).

Obesity was more common prior to diagnosis in patients with endometrial cancer (RR = 2.45, 95 % CI = 1.39–4.36), colon cancer (RR = 1.59, 95 % CI = 1.03–2.46) and kidney cancer (RR = 2.89, 95 % CI = 1.21–6.87). For breast cancer a non-significantly increased risk was seen above the age of 60 years (RR = 1.55, 95 % CI = 0.96–2.50). A lower non-significant risk of obesity was seen in patients with lymphoma (RR = 0.20, 95 % CI = 0.02–1.49) and non-melanoma skin cancer (RR = 0.45, 95 % CI = 0.18–1.12). For colon cancer this finding was seen only among males, while for renal cancer risks were higher in females and younger patients. Diagnosis of elevated blood lipids was similar among cancer cases and controls (RR = 1.00, 95 % CI = 0.93–1.08. High blood lipids were more common prior to diagnosis in patients with ovarian cancer (RR = 1.93, 95 % CI = 1.12–3.31). A significantly lower risk of high blood lipids was seen in patients with breast cancer (RR = 0.79, 95 % CI = 0.62–1.00). The lowest frequency of blood lipid abnormalities was seen for breast cancer in patients younger than 60 years of age at diagnosis, while for ovarian cancer a higher frequency of blood lipid abnormalities was seen for patients above 60 years of age at diagnosis.

The result presented is derived from the univariate models. In the multivariate analysis performed for each tumour type, where comorbidity diagnoses were simultaneously adjusted for, cases and controls were matched for age, gender and domicile, but the findings were essentially the same as in the univariate analyses. Whether our significant findings are causal risk factors or markers of disease risk remains to be determined. We want to caution against making far-reaching interpretations before the results have been confirmed especially with a longer risk time between comorbidity and cancer diagnosis. Our data already imply, however, that in order to assess disease risk (cancer risk) for a particular individual it is necessary to have information concerning lifestyle factors, genetic factors (family history and SNPs) and comorbidity as well as relevant risk biomarkers. We propose that future risk-assessment models use the design suggested in Figure 8.6. Genetic and lifestyle factors are already of importance early in life while comorbidity factors achieve increased importance with the greater age of the individual. We would like to emphasize that in current risk models for cancer, comorbidities are rarely, if ever, included.

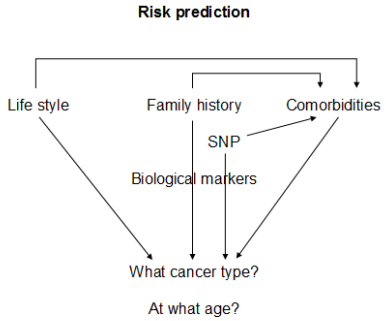

Figure 8.6. Risk assessment using lifestyle (environmental factors), genetic factors, comorbidities and biological markers to assess the risk of developing a particular cancer type at a given age. SNP = single-nucleotide polymorphism

Conclusions

In conclusion, the study confirms some previous findings concerning comorbidity and cancer and highlights some new ones. From a public health view avoiding overweight and obesity, as well as preventing type II diabetes mellitus, are important in preventing cancer and other diseases. Measures should be taken early on and should be based on healthy eating and physical activity patterns throughout life. Obesity, diabetes mellitus and blood lipid abnormalities are important comorbidities for distinct cancer forms and their prevention could have a substantial health impact on cancer and non-cancer diseases. Furthermore, this new knowledge concerning cancer and comorbidities may provide an insight into the mechanisms of tumour development. Postponing the onset of comorbidity may also prevent/postpone the diagnosis of cancer.

8.1.5 Study V: A population-based study of health care costs for patients and partners with lung cancer and of factors influencing survival in patients with non-small cell lung cancer (NSCLC) in Sweden

Introduction:
In Sweden lung cancer is the fifth most diagnosed cancer with about 3,500 new cases every year (2009). The incidence is increasing especially among women and nowadays they constitute about 51% due to changing smoking habits the last 50 years. About 50% of the patients are older than 70 years and about 70% are in a late stage of the disease (stage III b-IV). This year's Report to the Nation in United States documents the second consecutive year of decreasing lung cancer mortality rates among women. Lung cancer death rates in men have been decreasing since the early 1990s.

Previous studies have shown that the cost burden of lung cancer is high and varies according to treatment type. The national expenditures in US for lung cancer were highest for the initial care as well as for the last year of life whereas a smaller part was accounted for the continuing care. A Swedish study has seen differences in treatment activity between counties and how this was associated with survival . Several other studies, many of them recently, has been published about prognostic factors as treatment and comorbidities for survival but also including the aspect of quality of life and social inequalities. Another perspective of lung cancer related health care costs not yet fully investigated are the costs for the influence on relatives, for example the partner. In a recent study we found that partners of lung cancer patients had a significant increase in psychiatric diagnoses and in circulatory diseases leading to a significant increase in health care use.

The aim of this study was to examine and analyse all direct health care costs among patients and partners of lung cancer. The aim was also to examine factors influencing survival in patients with non-small cell lung cancer (NSCLC).

Methods: We used population-based data for monitoring health care costs, including in- and outpatient care for both patients and their partners. For each individual all healthcare contacts were monitored in relation to time periods before and after the date of the lung cancer diagnosis.
All data and calculations refer either to the population in the Southern Health Care Region in Sweden (1.8 million inhabitants) or to the population of the county of Skåne in this region (1.2 million inhabitants); see description about different subpopulations in the study (chapter 7.2.2). All persons diagnosed with lung cancer in the period 2000 to 2007 were identified via the Cancer Register of Southern Sweden.

Individual data were linked via the ten-digit personal identification number to the Population Register of Sweden, Regional Health Care registries including primary care, and National Health Care registries also including prescribed pharmaceuticals. Data on tumour stage and treatment types were obtained from the Lung Cancer Register. For each individual, healthcare costs were monitored related to the date of diagnosis. Using this method we calculated the costs for different time periods before and after diagnosis and proximity to death.

To analyse factors influencing survival/mortality risk ratios (RR) and 95 % confidence intervals (CI) for patients with NCSLC for the case in relation to all factors were calculated using Cox proportional hazard model, SPSS for Macintosh, version 19. In the multivariate analysis, each factor was simultaneously adjusted for.
Results: The major part of health care costs for lung cancer patients occurred during the first year following the diagnosis. A clear difference was seen between costs for survivors and patients who later died. Highest health care costs were seen for patients treated with endoscopic therapy of the bronchus. Health care costs were higher for operated patients compared to those with treatments only by chemotherapy or radiotherapy. Totally the costs were declining with higher stage, Table 8.1.

Partners had an increase in health care use both the first and second year following the patient's diagnosis of the lung cancer leading to an increase in health care costs.

Table 8.1. Health care costs per patient (Euro) during a period of two years before and two years after diagnosis stratified for kind of treatment and stage 2002-2005 in the county of Skåne.

	Stage											
Types of treatment	Not registered		Stage I		Stage II		Stage III		Stage IV		Total	
	Number	Cost/person	Number	Cost/person	Number	Cost/person	Number	Cost/person	Number	Cost/person	Number	Cost/person
No treatment	***19***	***16 652***	***34***	***32 294***	***6***	***20 411***	***91***	***25 004***	***165***	***20 282***	***315***	***22 726***
Surgery												
- only			274	34 374	27	39 657	19	41 898	8	43 963	328	35 478
- with chemotherapy			35	36 958	5	26 059	3	23 121	2	29 025	45	34 472
- with chemotherapy and radiotherapy (primary)			9	47 924	4	39 808	34	38 232	2	53 024	49	40 744
- with some different treatments			1	34 707	1	41 105	6	29 440	2	34 612	10	32 168
Surgery - total			***319***	***35 040***	***37***	***37 875***	***62***	***37 773***	***14***	***41 788***	***432***	***35 894***
Chemotherapy												
- only	13	39 757	19	40 228	11	37 358	169	32 673	335	30 737	547	32 012
- with radiotherapy (primary)	3	44 623	15	48 758	9	26 324	163	37 830	27	32 596	217	37 551
- with radiotherapy (metastasis)	2	52 394					3	25 106	138	28 649	143	28 907
- with radiotherapy (primary and metastasis)							15	33 575	38	30 704	53	31 516
Chemotheapy - total	***18***	***41 972***	***34***	***43 991***	***20***	***32 393***	***350***	***35 048***	***538***	***30 292***	***960***	***32 774***
Radiotherapy												
- primary	2	26 335	29	32 356	4	27 141	27	32 046	16	22 982	78	29 904
- metastasis							3	31 455	60	23 948	63	24 305
- primary and metastasis					1	32 034	2	32 298	15	35 243	18	34 738
Radiotherapy - total	***2***	***26 335***	***29***	***32 356***	***5***	***28 120***	***32***	***32 006***	***91***	***25 640***	***159***	***28 233***
Endoscopic therapy of the bronchus												
- only			1	56 605			1	17 845	3	45 158	5	41 985
- with other treatments			2	14 445			10	46 683	7	31 784	19	37 800
Endoscopic therapy of the bronchus - total			***3***	***28 498***			***11***	***44 061***	***10***	***35 796***	***24***	***38 672***
Total	**39**	**28 835**	**419**	**35 311**	**68**	**34 005**	**546**	**33 687**	**818**	**28 020**	**1 890**	**31 506**

A higher/lower mortality in patients with non-small cell lung cancer was mostly explained by surgery (primary) RR=0.39 (95 % CI 0.33-0.46), short waiting time (time between date of diagnosis and date of decision about treatment) RR=0.68 (95 % CI 0.62-0.74) and treatments by radiotherapy (primary) RR=0.87 (95 % CI 0.78-0.97. Lower survival was connected to no treatment RR=1.63 (95 % CI 1.40-1.88), tumour stage IV vs I-II RR=2.58 (95 CI % 2.20-3.02), tumour stage III vs I-II RR=1.77 (95 % CI 1.51-2.06), performance status 1, 2, 3 and 4 vs 0 with RR=7.43 (95 % CI 5.80-9.51) for grade 4, alcoholic related diseases RR=1.49 (95 % CI 1.12-1.97) and patients living in three specific geographic areas (F,C,A); RR=1.28 (95 % CI 1.12-1.46), RR=1.26 (95 % CI 1.05-1.50 and RR=1.20 (95 % CI 1.00-1.42).

Conclusions

Lung cancer is an important issue in terms of health care decisions. The cost burden of lung cancer and the survival in patients with NSCLC varies with the phases of the disease and with treatments. In this study we have elucidated different perspectives of significance when calculating costs for lung cancer. In the future, new treatments, especially new pharmacy, are to change the relationship between treatments, costs and survival. In future research this also needs to be considered, as costs of lung cancer are likely to increase. When planning for care and allocation of resources for care the impact on the partner should also be considered. It is of importance also further examine in what way results are affected by how the patient comes in contact with the health care system, the patient´s lifestyle and socioeconomic background or the health care system itself.

8.2 Additional reports and articles

8.2.1 Reports

The Southern Regional Health Care Committee initiated a study of the process for the provision of cancer health care in southern Sweden. The aim was to examine and analyse incidence, health care consumption, outcomes and costs among persons with common types of cancer including colon, rectal, lung, breast, or prostate cancer. The investigations have resulted in four reports, published on the Southern Regional Health Care Committee´s website, http://www.skane.se/templates/Page.aspx?id=208634 .

The first report published in 2008 showed large differences in incidence and survival for patients diagnosed with cancer 2000-2005 due to in which geographical area the patients were living, especially for prostate and lung cancer. Therefore, a wider study with longer time period (2000-2007) was done 2009 analysing all types of cancer and with specification of 18 types of cancer. In the meanwhile two other reports were done to analyse the visits to doctors before and after the patient got the cancer diagnosis and whether other diagnoses/comorbidities were associated with the diagnosis of cancer.

In the three first reports, with a design as for the articles (see chapter 7.1 Design), individual data from period 2000-2005 was used for five cancer forms (colon, rectal, lung, breast, and prostate). Totally, the processing covered 27 188 reported tumours for 26 800 persons. In the first report was presented results from the patient´s perspective per county council/districts with indicators as incidence, own-produced healthcare, costs and survival. All indicators pointed out large differences. Differences in incidence may sometimes be explained by differences in screening practices but there is often a need to further explore the reasons by taking into considerations, for instance, occurrence of risk factors or clinical practice in setting diagnosis. High significantly differences in survival was presented for prostate and lung cancer.

The health-care for others diseases/cancer are included in the cancer-case. During 2005, the total costs in Southern healthcare region was approximately 1 200 million SEK for persons with incidence this year or earlier years in presented cancer forms. More than half the sum was not related to health care for stated cancer diagnosis. The total care cost per person during a period of six years (3 years before and 3 years after) was per person from approximately 360 000 SEK (rectal cancer) to 185 000 SEK (prostate cancer). Per 100 000 inhabitants, the care costs during a year (prevalence) can be calculated from 21 million SEK (prostate cancer) to 7 million SEK (rectal cancer).

The number of visits to doctors per patient one year before and one year after cancer diagnosis was presented in report 2. The sample was patients in the county council Skåne (totally 7,143 persons) Patients with lung cancer had most visits (10.3) and during the two-year period nearly half of the visits (44 %) were related to cancer diagnosis. Patients with colon cancer had fewer visits (6.2) and of these 22 % were associated with cancer diagnosis. Patients with lung, rectal and colon cancer had the highest average length of stay (ALOS) one year before and one year after cancer diagnosis (31, 26, 26 days respectively), while patients with breast and prostate cancer had nine and seven days respectively. Almost 60 % of bed days were for patients with colon, rectal and lung cancer and were related to cancer diagnosis. Visits to doctors up to 48 months before and 12 months after the date of diagnosis in 2004-2005 for the cancer patients in Skåne were examined. Figure1 shows the average number of visits per patient, month and cancer type up to 12 months before and 12 months after diagnosis. The visits for patients with lung and colon cancer increased 4-5 months before cancer diagnosis but there was no increase in the number of visits by patients with breast cancer until the last month before diagnosis and occurred most visits the month after diagnosis.

The number of visits to doctors in our study was compared with the pattern of visits for the general population in Scania (2003). All cancer types showed more visits than calculated especially 1-12 months before cancer diagnosis. The index for this period was: breast cancer 112; rectal cancer 124; prostate cancer 137; colon cancer 161 and lung cancer 188. All cancer types, apart from rectal cancer had higher index even 13-48 months before diagnosis. Men had fewer visits than women in the periods observed except for men with rectal cancer 1-12 months prior to diagnosis.

We also investigated whether specific patterns of health-care consumption could be a sign of a later cancer disease. Of the whole population in Skåne, in the age group 25 years and above 3.8 per cent had 10 or more visits to doctors during one year (2003). During the following two years (2004-2005) 1.21 per cent of these persons were diagnosed with one of the cancer diseases studied. In the same age group with less than 10 visits to doctors during one year, 0.88 per cent were diagnosed with one of the cancer diseases studied. This result showed that this small group within the population, with 10 or more visits to doctors during one year, had a 38 per cent higher risk of developing cancer disease later.

Using population based register data from specialist and primary care in our health care region comorbidity in the form of anaemia, hypertonia, diabetes, rheumatoid arthritis, chronic obstructive pulmonary disease, and alcohol related diseases for patients with colon- , rectal-, lung-, prostate and breast cancer and survival were studied. Altogether 2047 colon cancer cases, 985 rectal cancer cases, 2017 lung cancer cases, 3578 breast cancer cases and 5106 prostate cancer cases diagnosed 2002-2005 were included. Results were age and sex adjusted and one year survival was calculated. Comorbidity was studied prior to cancer diagnosis and in order to compare with the general population all first comorbidity diagnoses within 90 days were censored.

The prevalence of the chronic diseases in the general population was for all ages; diabetes 3.2%, rheumatoid arthritis 0.5%, hypertonia 6.8%, anaemia 1.1%, KOL 1.0% and alcohol related diagnoses 0.7%. Patients with colon and rectal cancer had a higher prevalence of anemia, and diabetes. Patients with lung cancer had a higher prevalence of anaemia, KOL, diabetes, rheumatoid arthritis for both men and women and for men also a higher prevalence of alcohol related diseases. Except for alcohol related diseases in females with breast cancer comorbidity for the above diseases were not significantly elevated for breast or prostate cancer. For all diagnoses hypertonia were significantly lower than in the general population.

Survival of the different cancer diagnoses was not significantly related to the comorbidity except for a tendency of worse survival for patients with alcoholic related disease. The prevalence of some common chronic diseases is elevated especially in colon-, rectal and lung cancer patients. The comorbidity does not seem to affect short term survival of the cancer patient except for alcohol related diagnoses. Our study also indicates the necessity to have all levels of care included in the study base of comorbidity and also emphasizes the need to censor time prior to diagnosis when comparing data with the general population.

In the fourth report, presented 2009, the study population increased with 2 years and included 2000-2007. Results were presented for incidence, survival and mortality for all types of cancer with specification of 18 types. On average, the incidence had increased by 2.4 per cent annually during the period, highest for lymphoma (10,5%), brain tumours (gliom) (5,4%), melanoma and kidney cancer (5,1%). One year survival increased with 6,5 per cent during the whole period.

It was significantly higher risk for mortality in men in these types of cancer; rectal 33 %, colon 20 % lung 16%, pancreas 13% and significantly lower risk for mortality in melanoma: -37 %. Compared with the domicile where people live near the University hospital in Lund, all other domiciles hade totally higher risk for mortality (4-14 %).

The significant results of the domiciles per types of cancer wore:

- Blekinge; prostate 49 %, lymphoma 43 %
- Southern Halland; prostate 23 %, colon 17%
- Kronoberg; ovary 38 %, lung 35 %, prostate 32 %
- North east of Skåne; lymphoma 58 %, liver 54%, prostate 29 % melanoma -33 %
- South west of Skåne; liver 34%, prostate 26 %
- North west of Skåne; lung 32 %, prostate 30 %
- South east of Skåne; brain (glioma) 51 %, liver 39%, prostate 30 %

8.2.2 Articles

As described in chapter 7.1 Design, studies have been done about sickness absence among cancer patients in the pre-diagnostic and the post-diagnostic phases of five common forms of cancer and on sick leave of spouses to cancer patients before and after diagnosis.

Sickness absence among cancer patients in the pre-diagnostic and the post-diagnostic phases of five common forms of cancer

Introduction
Since the survival from cancer is constantly improving and prevalence of cancer in the working population is likely to increase [1], it is of great importance to get increased knowledge about the impact of different types of cancer and cancer treatment on the patients' working ability. One way to measure sickness is by using data on sick leave/sickness absence. The purpose of this study was to observe sickness absence before and after the cancer diagnosis among cancer patients with five common types of cancer.

Methods
In this population-based cohort study, we used Swedish health care and social insurance data. We observed sick leave in the pre- and post-diagnostic phase among patients with colon, rectal, breast, prostate, or lung cancer (n=2,738). We also identified reference subjects without cancer (total n=12,246) who were individually matched for age and gender for each specific cancer cohort in order to compare sickness absence between patients with a specific form of cancer and the background population without cancer.

Results
Lung cancer patients had the highest increase in sick days both pre- and post-diagnosis and prostate cancer patients had the lowest increase. Irrespective of the form of cancer, cancer patients had significantly more sick days in the post-diagnostic phase compared to their reference subjects, ranging from 5 (prostate cancer) to 12 times the amount of sick days (colon and lung cancer). One year post-diagnosis, less than half of the cancer patients were on sick leave, except for lung cancer patients where 63% were still on sick leave.

Conclusion
Sick leave among cancer patients seems related not only to the cancer diagnosis and its treatment but also to the prodromal illness in the pre-diagnostic phase, especially for forms of cancer with heavier symptom burden such as colon and lung cancer. Although cancer results in substantial increase in sick leave, it is important to acknowledge that a major part of cancer patients return to work within 1 year after the cancer diagnosis.

Sick leave of spouses to cancer patients before and after diagnosis

Introduction
Both the patient and their family are affected by the disease and the treatment experience after a diagnosis of cancer. The spouse of a person affected by cancer is often the most important person in providing both emotional and practical support during the time of disease and treatment. The significance of this support increases as a growing number of cancer treatments are delivered in open care. To be a spouse to a cancer patient is often associated with a substantial impact in daily life. Besides worries about the disease and treatment outcome, practical duties often increase the burden. Furthermore, many spouses undertake major care giving tasks. The burden of care giving may include not being able to perform employment work as usual, leading to both psychosocial as well as financial consequences. Our objective was to evaluate sick leave in spouses of cancer patients before and after the diagnosis.

Material and methods
Using Swedish population-based registries, we studied sick leave of spouses to patients with newly diagnosed colon, rectal, lung, prostate, or breast cancer. We identified the cancer patients via the Swedish Cancer Registry and obtained information of their spouse through linkage with the population register. We assessed the number of sick leave episodes and sick days one year before until one year after the spouses' cancer diagnosis by cross-referencing with Swedish Social Insurance Agency data. We also compared the number of sick days of spouses with the general population adjusted for age, sex and partner status.

Results
In general, spouses (N=1,923) to cancer patients had an increase in the frequency of new episodes of sick leave in the months before and after the cancer diagnosis. Spouses of lung cancer patients had most sick leave episodes, and the largest number of sick days per person. In comparison to the general population, spouses in the lung cancer group also had the highest standardised sick day ratio 1.76; 95% confidence interval 1.24-2.40. The corresponding risk for spouses in other groups of cancer was not significantly increased.

Discussion
In Sweden there is often increased sick leave of spouses to cancer patients. It may be due to emotional stress and physical reactions that follow with cancer which needs to be further explored in order to provide adequate support and care.

9 DISCUSSION

9.1 Methodological considerations

The strengths and limitations in the papers are summarized in Table 9.1.

Table 9.1. Methodological considerations regarding strengths and limitations

	Strengths	Limitations
All papers	Population-based national/regional register data linked together by the unique personal identification number. For each individual, patients as well as partners, health care consumption, diagnoses, health care costs and survival/mortality were monitored in relation to the patient´s date of diagnosis. Analyses were stratified for different time periods in days before and after diagnosis and proximity to death.	No data for • Municipal care • Sickness absence (in additional paper) • Pharmaceuticals for patients in studies • Production loss • Not measurable costs No adjustment for socio-economic status. ABC-costs only for the university hospitals. Relatively short time periods.
Paper I		Not all types of cancer. Partner is defined living with the patient at the patient´s date of diagnosis. No other relatives were studied.
Paper II	Large standardised group of control-persons. Excluding the risk time of the 90 days immediately prior to the cancer diagnosis.	Short time period depending on no registration of diagnoses in primary care before 2004. The reasons for a low cancer incidence not further studied.
Paper III	Data for both patients and partners giving a more complete description. Health care costs for survivors and deceased. Health care costs for prostate cancer patients with different treatment types stratified by accumulated Gleason groups.	No diversification (break down) of costs per treatment type No adjustment for time at risk for deceased when stratifying costs by Gleason score.
Paper IV	Large standardised group of control-persons. Excluding the risk time of the 90 days immediately prior to the cancer diagnosis. Uni- and multivariate analyses. Expanded time period.	Short time period for diagnoses in primary care. Reverse causality? Causal risk factors or markers?
Paper V	Data for both patients and partners giving a more complete description. Health care costs for survivors and deceased. Health care costs for lung cancer patients with different treatment types (including combinations) stratified by tumour stage. Many factors potentially influencing survival for patients with NSCLC studied.	Loss of data in quality register. No diversification (break down) of costs per treatment type. No adjustment for time at risk for deceased when stratifying costs by tumour stage.

The findings reported in this thesis are in accordance with results from previous studies. The strengths of the design with these three main subjects ought to mean that conditions are not manipulated by the researcher (66) :

- Population-based national/regional register data linked together by the unique personal identification number.
- For each individual, patients as well as partners, health care consumption, diagnoses, health care costs and survival/mortality were monitored in relation to the patient´s date of diagnosis.
- Analyses were stratified for different time periods in days before and after diagnosis and proximity to death.

Both the population-based cancer register and in- and outpatient registries in the study region have a well-documented almost complete coverage (62, 63) . Using population-based registries in this thesis, the Swedish Cancer Register is the base-register in all papers to which many other registries are linked. In this register approximately 98 per cent of the cases are morphologically verified national as well as regional. The reliability of the diagnosis may vary with the hospital, department and/or physician concerned; this may add to a geographical variability, though the structure of the public health system is homogeneous (39) .

The limitations in this study with no data for municipal care, sickness absence (in additional paper), pharmaceuticals for patients in studies, production loss and not measurable costs are of importance in different ways. Lack of data from municipal care means that the complete picture of health care and its costs for patients and partners is not showed. Missing pharmaceutical data are information bias in hospital health care. No data of production loss and not measurable costs means that the total cost in the society for patients and partners due to the cancer patients not are measured.

Information about comorbidity was obtained through the outpatient and inpatient registries. In these registries, physicians record the main diagnoses and up to seven other diagnoses for which a patient is investigated and treated. This approach is new compared with other previously published register-based studies in Sweden (63) where information was obtained only from inpatient registries and therefore underestimated the comorbidity, especially in milder disease cases and in individuals suffering from a single comorbidity.

However, a possible bias in both out- and inpatient registries could be that the comorbidities are not registered because the doctors forget or refrain from registering a diagnosis such as dementia (55) . The extent of underregistration is not known, but the introduction of economy systems based on diagnosis-related groups and better education in coding and registration have limited this problem because payment is related to care of all diagnoses. Furthermore, we have no reason to believe that a possible doctor bias regarding a dementia diagnosis would affect the cancer populations differently from the controls.

It was not possible to obtain a complete population-based coverage of comorbidities through registries before 2004. In paper IV, the emphasis was therefore put on the time period up to 4 years before diagnosis of cancer, as this also included the comorbidity diagnoses registered in primary care. Including comorbidity diagnoses from 1998 onwards allowed us to compare the association between the comorbidity and cancer for the short and long follow-ups. We tried to reduce possible bias from detecting more other diseases close to a cancer diagnosis by excluding the risk time of the 90 days immediately prior to the cancer diagnosis. Controls were matched to each case by age and gender and needed to be alive at the time the case received the cancer diagnosis, living in the same area and without a cancer diagnosis themselves. In our study, we could estimate what the overall cancer effect of an increased diagnostic surveillance or the disease effect would have been if we had not restricted the risk time to 90 days prior to the cancer diagnosis for the time period up to 4 years; a diagnosis of diabetes would have increased the risk of cancer from 1.14 to 1.28, a diagnosis of

obesity would have decreased the risk of cancer from 1.07 to 0.98 and a diagnosis of abnormal blood lipids would have increased the risk of cancer from 1.00 to 1.06.

A limitation in paper I is that we were only able to include the partner/spouse, and there might be other significant persons who can play an important role in supporting the person with cancer. The role of parents, siblings, children, and presence of close friends also needs to be explored. These are persons in the social network which might have a significant impact on both the person with cancer and the partner. The role of the partner/spouse in relation to survival of the patient with cancer will be evaluated in a coming study. In this study, information on former life partners (divorcees, dead) is missing, and no data is available on divorce rates of the sample during the period. Attrition due to moving out of the region was analysed and was found to be lower than 1%. The health care use and health care costs for the partner of patients with cancer have not been explored before this study. This population-based study with years of follow-up study gives strength, and the findings contribute, to the knowledge about the indirect costs of cancer.

Methodological considerations to be made in paper III and paper IV might be the limitation that data does not include costs for municipal care. With both the ageing trend in the population and thereby increasing number of elderly with prostate or lung cancer, and the new possibilities to take care of the patients at home, it is important to also consider those data in future studies. The results give new knowledge about total health care costs related to different treatment types, isolated or combined, but do not tell the actual treatment costs. Another limitation might be that we did not adjust for time at risk for the deceased when stratifying health care costs by Gleason score (prostate) or tumour stage (lung), leading to a probable underestimation of health care costs for patients with higher Gleason score/tumour stage.

9.2 Main findings

9.2.1 Cancer and comorbidities

The results in paper II confirms previous findings that patients with dementia have a lower risk of cancer. Dementia has been found to be associated both with a reduced cancer morbidity and mortality in other studies (45, 50, 54, 55, 68-71). The investigations have been both clinical and autopsy studies. The authors have explained that these results possibly are due to a biological factor (45, 55, 68, 72) or a diagnostic bias (50, 68).

Overall a diagnosis of dementia was significantly less common among the cancer cases. The reduced risk was more pronounced for patients older than 70 years than for patients younger than 70 years. A significantly lower risk of dementia was seen in patients with colon cancer, lung cancer, melanoma, prostate or urinary bladder/tract cancer and no diagnosis of dementia was found among patients with cervical cancer, brain tumours and leukaemia. Non significantly low risks were seen for all other studied tumour types. The low risks were most pronounced for tumours developing within the body compared to those presenting closer to the body surface. Our data, we believe, suggest that the main reason for the lower cancer risk is due to underdiagnosing of cancer for the following reasons. Firstly, all cancer types showed a reduced relative risk, secondly, tumours within the body showed the lowest relative risk compared with malignancies presenting closer to the body surface and finally the relative risk was lowest for older individuals.

The reason for the low risk if due to underdiagnosing could be discussed. It could depend on the patient him/herself not being able to communicate the symptom of cancer. It could also be due to the physician or the family refraining from investigating symptoms of the patient with dementia. Further studies need to address these questions in more detail also for other diseases than cancer. Of course it could be discussed if a hesitant attitude in investigating symptoms of tumours in patients with dementia is fully appropriate especially if the patient is above 70. The question, however, raises important moral and ethical aspects, and in the forthcoming years there will be an increasing population of old age men and women of whom an important proportion will suffer from dementia. Pre-existing dementia affects cancer care and is associated with high mortality, mostly from non-cancer causes (73), and dementia significantly increases the mortality of patients with cancer (74). Another Swedish study found that in extreme old age, Alzheimer disease and vascular dementia influence the mortality rate considerably (17).

The overall cancer risk was significantly increased by 14 % among diabetes patients, showing a significant increase for colon, liver and pancreatic cancer and an almost significant increase for breast cancer and tumours of the bladder and urinary tract. These findings were presented in paper IV. We did not have information about type 1 and type 2 diabetes but we separated effects for gender and age. In our study patients younger than 60 years, in general, had a stronger association with diabetes and pancreatic, liver and colon cancer. Looking at different time periods before cancer diagnosis, a significantly increased risk was seen both in the short- and long-term for liver, pancreatic and colon cancer. However, for pancreatic cancer a higher risk was seen for diabetes close to diagnosis, which could imply a reverse causality as suggested by others (51, 75, 76). In breast cancer, a significantly increased risk was seen only for the short period. This is of considerable interest as other studies with short-term patient follow-up (77-79) have found an increased risk for breast cancer possibly associated with an insulin analogue therapy. Whether this is related to the therapy or the disease itself, through hyperglycaemias for instance, needs further study. It is to be noted that as the use of long-acting insulin analogue was accelerated from 2003 onwards, it can only affect risk in the short-term in our study.

For various tumour types, diabetes has been found to be associated with both an increased and a reduced cancer risk (44). In observational studies consistent evidence has been obtained of

associations between diabetes and increased risk of cancer of the pancreas, liver, endometrial and colon while for esophagus, stomach, prostate and breast cancers the limited data available are inconsistent (58, 80, 81). This inconsistency could be due to small sample size, varying study designs and study populations. Other problems include difficulties in separating the effects of type 1 from type 2 diabetes. Diabetes therapies could also have implications, for example, the use of metformin has been shown to reduce cancer incidence by up to 30 % (82) while the use of insulin, such as the long-acting insulin analogue glargine (Lantus), may increase cancer risk (77-79, 83). The observations presented require further analysis and evaluation, and are likely to open up a much wider debate, already started by Smith and Gale in an editorial article in Diabetologia (84).

Patients with diabetes had a significantly reduced risk of prostate cancer, especially if the case was below 65 years of age. A low incidence of prostate cancer in diabetes has been seen both in previous studies summarized in meta analyses (47, 85) and in findings in some recent studies (58, 86, 87) [. Corroborating these findings, allele variants of genes TCF2 and JAZF1 associated with type 2 diabetes have recently been shown to be associated with a reduced risk of prostate cancer (88) linking molecular biology to epidemiological results. However, it is unlikely that all the inverse relations between prostate cancer and diabetes can be explained by these recent genetic findings. Longstanding diabetes in men could be associated with lower testosterone levels (47, 49, 86), which could also reduce the risk of developing prostate cancer. More studies are also needed to distinguish between the different diabetes types.

Obesity has most clearly been shown as a risk factor for esophageal, pancreas, colorectal, breast (postmenopausal), endometrial and kidney cancer (89-91). As presented in paper IV, obesity was in our study significantly associated with colon, endometrial and kidney cancer while esophageal cancer was not studied separately. There was a high, non-significant risk in the case of liver cancer and postmenopausal breast cancer. The colon cancer risk was only seen in males, while the findings for kidney cancer were strongest for females and for patients less than 60 years of age. In the meta-analysis of BMI and incidence of cancer, Renehan et al. (91) found that for persons with higher BMI men had a higher risk of colon cancer than females. A slightly higher risk with higher BMI was also seen in the same meta-analysis for females than males in the case of renal cancer. We have no clear biologically explanation for the finding of gender differences concerning obesity in colon and renal cancer. Hormones could be involved and further studies are needed to clarify and confirm the findings. In our study, an obesity diagnosis elevated the overall cancer risk non-significantly by 9 %. It is clear that to be registered by the physician as an obese patient, a BMI of 30 kg/m2 or more is needed. Therefore, our study is unable to assess the relationship between overweight and cancer risk.

In paper IV was also presented that the lowest frequency of blood lipid abnormalities was seen for breast cancer in patients younger than 60 years of age at diagnosis, while for ovarian cancer a higher frequency of blood lipid abnormalities was seen for patients above 60 years of age at diagnosis. The question of whether low serum cholesterol is associated with a higher incidence of cancer has been debated as a result of studies indicating a higher risk of cancer in individuals taking cholesterol-lowering drugs (92). Not all studies, however, have been confirmatory and a reverse causation has been discussed for the finding in some studies that a low cholesterol level has preceded tumour diseases in close proximity in time (93, 94). It has been hypothesized that the hypercholesterolemia was caused by the tumour disease itself (92). The tumour diseases implicated in low cholesterol levels mainly involve lung cancer and colon cancer in males and breast and cervical cancer in young women (92). Our study, involving an abnormal blood lipid picture, has a different design. A significantly low risk of breast cancer, especially for individuals below 60 years of age, does not immediately imply that hypercholesterolemia is the relevant risk factor. It means that fewer breast cancer patients have abnormally high levels of blood lipids. In most cases high blood lipids imply, hypercholesterolemia. It is, however, noteworthy that the effect in other studies looking at low cholesterol levels in breast cancer has occurred in cases under 50 years of age (95, 96).

In our study, we also found that a significantly higher risk of abnormal blood lipids was found in patients with ovarian cancer. We have not been able to find studies, which assess this question other than Helzlsouer et al. and Bjørge et al. (97, 98) who also found increased risk of high cholesterol levels and ovarian cancer. It is interesting that breast cancer and ovarian cancer show opposite risks with abnormal blood lipids. In ovarian cancer, the risk was strongest for older patients. The mechanism is unknown and the question of whether lipid-lowering treatment would favourably reduce ovarian cancer risk or affect the prognosis has not been answered. No significant effect of blood lipids on cervical and lung cancer was seen although the risk of cervical cancer reached 1.55. It is worth noting that the overall cancer risk was not elevated in individuals with an abnormal blood lipid profile.

Our finding that breast cancer patients have fewer diagnosis of abnormal high blood lipids could possibly also be due to reverse causality as the finding only was significant for the time interval within 4 years of the breast cancer diagnosis. The association between high blood lipids and ovarian cancer however is new and cannot be explained by reverse causation. It should be noted that in our study, obesity and abnormalities in lipids signify disease levels of these factors and we cannot therefore assess the importance of weight and lipid levels found in the normal range.

9.2.2 Cancer and survival

A higher/lower mortality in patients with non-small cell lung cancer was mostly explained by surgery (primary), short waiting time (time between date of diagnosis and date of decision about treatment) and treatments by radiotherapy (primary). Lower survival was connected to no treatment, tumour stage, performance status, alcoholic related diseases and patients living in three specific geographic domiciles. These results are presented in paper V.

It is well-known that survival/mortality is due to factors as age, surgery, short waiting time, treatments by chemotherapy or radiotherapy, no treatment, tumour stage, performance status and different comorbidities (7, 8, 20-23, 25-27, 30, 31, 34, 41, 46, 52, 60, 61, 99). A lower survival for men than for women has been recognised previously with regard to a number of tumour diseases (11, 34). Smoking is the most important risk factor for lung cancer and causes substantial comorbidities but overall lifestyle may also influence, especially for psychiatric diagnoses (100). We could in our study show the relationship between many of these factors for patients with NSCLC but still we also could see some differences due to patients living in a specific geographic area.

Many studies have discussed whether observed social class differences in incidence and survival are influenced only by lifestyle-related risk factors such as diet, physical exercise, alcohol consumption, smoking etc or whether part of the variation is attributable to socio-economic factors (35, 101). Two studies presented from the National Board of Health and Welfare in Sweden shows from a socio-economic standpoint (based on education levels) firstly that both male and female patients with rectal and lung cancer, and with low socio-economic status, have a higher incidence than other patients (102) and secondly they present large differences in one-year survival between these socioeconomic groups (103). Other studies have reported that persons with low socioeconomic status consult care in a later stage than patients with higher socioeconomic status (104). Berglund et al have recently presented three studies founding evidence of a social gradient in the clinical management with lung cancer both in central Sweden and in South East England and that patients with high socioeconomic status were more likely to undergo an active treatment (18, 19, 105).

We believe, that the differences between socioeconomic groups mostly are explained by factors we have analysed such as comorbidities, smoking, performance status, stage, treatment etc. combined with lifestyle related risk factors. In a recent study we have presented a risk-assessment model for risk prediction based on lifestyle (environmental factors), genetic factors, comorbidities and biological markers (99).

The overall mortality in lung cancer in the population in the Southern Health Care Region was also studied. Area C had the lowest overall mortality combined with the lowest incidence in lung cancer but the highest mortality among patients with diagnosed lung cancer. This fact needs to be studied more. We already know that patients living in areas near university hospitals have been diagnosed in an earlier stage compared with patients from other areas (20, 31). To be able to achieve more equal care, the geographical differences in survival need to be explored further to discover the extent to which the observed differences are due to the occurrence of risk factors, tumour biology, attitudes to seeking health care, indicators for treatment, level of resources including competence, compliance to treatment, performance status, lifestyle and other socioeconomic factors.

Our results also suggest that survival rates are improved for those living with a partner compared to those living alone, which is supported in previous research showing that excess mortality for never married compared to married has increased steadily (presented in paper I). This is especially seen for men (106). Altogether it implies the importance of having a partner or another relative/friend when following a cancer therapy regimen.

9.2.3 Impact on partners´ health

Health care use for partners increased in terms of in-patient care after the cancer diagnosis. The increase was significant for partners of patients with colon cancer the first year after the cancer diagnosis. A significant increase was also seen the second year for partners of patients with colon cancer and lung cancer. Diagnosis in total among partners increased the year after the cancer diagnosis. The largest increase was seen for psychiatric diagnoses. The increase was significant for the total sample, with significant increases for partners of colon, lung, and prostate cancer patients.

Health care costs increased the first and the second year after the cancer diagnosis in all five diagnosis groups. When comparing with consumers prize index, the increase was higher from the time of the diagnosis and for the two following years. In comparison to the general population standardized for age, sex and marital status, male partners had a higher increase than female partners. Health care costs for partners were in general lower than health care costs for the standardized population. Younger male partners (25 to 64 years) had a larger increase compared to the general population.

The framework for this study was that a substantial part of previous research on partners of cancer patients have shown that partners are affected by the cancer diagnosis, in terms of psychosocial distress and psychiatric morbidity. The literature review indicates several psychosocial distresses which might explain some of the increased health care use in our study (107-113). The overall pattern of the findings of this study was that health care use, and consequently health care costs, increase for the partners of cancer patients in the period after the cancer diagnosis.

The largest increase of diagnoses among partners was seen for psychiatric diseases, especially for partners of patients with colon and lung cancer with two to three times more psychiatric diagnoses. Differences between the studied groups of cancer diagnosis were seen. This might have several explanations, including differences in disease state, survival rates, age, and sex. The symptoms and severity of the cancer might differ substantially, where several breast cancer patients were diagnosed in the screening situation whereas patients with colon, rectal, and lung cancer might have more advanced disease with advanced symptoms at the time of diagnosis. Previous research has shown that symptoms of depression increase in partners when physical symptoms in the cancer patient aggravate (114, 115) and when the partner's concern for the patient with cancer increases (116). Being an informal caregiver of the spouse with cancer, which may be the situation when the cancer is advanced, has also been found to be associated with increased psychological morbidity (107, 110, 113-115, 117). The higher number of psychiatric diagnoses needs to be scrutinized to exclude that the diagnoses are a surrogate for psychosocial problems in the family or a way to handle increasing demands of help with practical issues such as transportation, medication, hospital visits, and household chores. However, partners of patients with advanced cancer seem to have an increased risk of psychiatric morbidity.

Apart from the psychiatric diagnoses, an increase was seen for circulatory diseases (partners of patients with lung cancer) and muscle diseases (especially partners of patients with rectal cancer). One must consider the possibility that some of the somatic conditions might be characterized as psychosomatic. It might also be that the increase in muscle diseases in relation to other morbidity could be explained as a diagnosis to enable sick leave. The pattern of sick leave by partners of patients with cancer will be further explored in a forthcoming study. Differences in sex were seen as health care costs increased more for male partners than for female. The increase was especially noticeable in the groups of younger male partners (age, 25 to 64 years). This has to be related to the fact that women in general have higher health care costs compared with men. Sex differences have been found in previous research, but the literature is inconsistent. One study reported better quality

of life for male partners of patients with cancer than for female partners (118). In another study of patients with colon cancer and their partners, both male partners and male patients were found to be more distressed than their wives. (119). In contrast, two other studies showed that women, regardless of being patient or partner, reported more distress related to the cancer (109, 120).

Furthermore, it is reported that being a female spouse caring for a cancer patient with advanced disease is associated with higher likelihood of experiencing depression (110). Sex differences seem to be a complex issue that cannot be isolated as a single factor, and which might be related to those cancer diseases requiring more demanding care at home, but also related to other factors such as age or other contextual variables. An unexpected finding in our study is that partners of patients with cancer had lower health care costs compared with the general population. We sought explanation, but the finding was largely unexplained. It might be that the partner has more focus on the person with cancer before and during the period of cancer diagnosis, disease, and treatment, and less focus on his or her own health. However, a change in the pattern of health care use was seen especially in terms of inpatient care (hospital stays and days in hospital). An increase of inpatient care was seen most obvious in the second year after the cancer diagnosis among partners of patients with colon and lung cancer, and therefore seems to be correlated to diagnoses with lower survival rates. This might be related to the psychological burden, but it could also be a result of having set the own health aside for a period of time.

9.2.4 Cancer and costs

Prostate and lung cancer
Findings from this study provide additional information about all direct health care costs related to prostate (paper III) and lung cancer (paper IV) in different phases of the disease including the pre diagnosis phase. The major part of health care costs for these groups of cancer patients occurred during the first year following the diagnosis. Costs related to the prostate cancer diagnosis in the pre diagnosis phase are probably explained by the delay in registration of the diagnosis, which sometimes is done a few weeks after the actual time of diagnosis. For lung cancer patients these costs are probably mostly explained by the difficulties to decide the actual lung cancer diagnosis in time. The patients have many other diagnoses, especially related to the respiratory system, and many have bad performance status but it can also depend on a delay in registration of the diagnosis as for prostate cancer patients.

A clear difference was seen for cancer patients between costs for survivors and costs for those who later died. Findings from this study about costs in different phases of the disease are in accordance with previous research, showing that the two events with highest costs are the time of the diagnosis and the final year (37). Health care costs for survivors decreased with time from diagnosis, and costs related to the cancer diagnosis also decreased. This is concomitant to previous prevalence based research on health care costs for prostate and lung cancer, showing progressively lower costs the second and third year following the diagnosis (4, 24, 36, 121-125) . However, future studies need to focus the impact on costs that new treatment options might have had.

When comparing costs for prostate cancer with costs for breast cancer, a clear difference was seen in the first year following the diagnosis with higher costs for breast cancer. As breast cancer treatment is more intense during the first year this was not unexpected. When comparing costs for lung cancer with costs for prostate cancer, a clear difference was seen in the first year following the diagnosis with much higher costs for lung cancer. As lung cancer treatment is more intense during the first year this was not unexpected either due to that one-survival is not so high.

Health care costs for prostate patients increased with higher Gleason score in the year following the diagnosis. Higher health care costs were seen for patients treated with primary radiotherapy. Health care costs were higher for patients with curative treatments compared to those with palliative treatments. The differences in costs between lung cancer patients with different treatment types stratified by compressed stage groups are rather small. If we look at survival (in days) we have mentioned one example; it is higher figures for operated patients in stage IV compared with those in stage II (567 and 449 respectively). One explanation can be that patients operated for metastases in the brain are very costly but further and deeper studies are necessary to explain these figures. It is unknown how the methodological problem with spare or none data of pharmaceuticals for patients in studies have affected the results for both prostate and lung cancer patients.

Few studies have used a population-based approach and healthcare consumption, outcome and costs on an individual level have seldom been studied (15). Recently one article about cost efficiency of university hospitals in the Nordic countries and a report from SINTEF about costs of cancer in the Nordic countries (10, 67) have been published giving many examples in difficulties to calculate the health care cost per patient. Our data provide a baseline for further studies of the effects of the new targeted therapy. One important question for the future is how to prioritize limited resources and how to move resources from treatment to prevention (2-4, 6, 8, 9).

Partners to both prostate and lung cancer patients had an increase in health care use both the first and second year following the diagnosis of the cancer patient leading to an increase in health care costs. In comparison with partners to prostate cancer patients, health care costs were 22-35% higher for partners to lung cancer patients with increasing costs every year for both groups. Increases were

significant compared to costs for the general population, matched for gender, age and marital status. Younger partners (25-64 years old) had a larger increase than older partners (> 65 years).
The cost burden of cancer varies along the different phases of the disease. Partners to cancer patients might be affected by their own health with an increased health care use as a consequence. This should be considered when calculating the cost burden of cancer. The partner can be of great importance for the cancer patient in providing both practical and emotional support.

10 General summary and future perspectives

The study confirms previous findings that patients with dementia have a lower risk of cancer. Because the effect was seen for all tumour types and especially for patients older than 70 years and since the deficit was more pronounced for patients with tumours situated within the body, the data suggest that malignancies are underdiagnosed for persons with dementia.

From a public health view avoiding overweight and obesity, as well as preventing type II diabetes mellitus, are important in preventing cancer and other diseases. Measures should be taken early on and should be based on healthy eating and physical activity patterns throughout life. Obesity, diabetes mellitus and blood lipid abnormalities are important comorbidities for distinct cancer forms and their prevention could have a substantial health impact on cancer and non-cancer diseases. Furthermore, this new knowledge concerning cancer and comorbidities may provide an insight into the mechanisms of tumour development. Postponing the onset of comorbidity may also prevent/postpone the diagnosis of cancer.

Whether our significant findings about comorbidity and cancer are causal risk factors or markers of disease risk remains to be determined. We want to caution against making far-reaching interpretations before the results have been confirmed especially with a longer risk time between comorbidity and cancer diagnosis. Our data already imply, however, that in order to assess disease risk (cancer risk) for a particular individual it is necessary to have information concerning lifestyle factors, genetic factors (family history and SNPs) and comorbidity as well as relevant risk biomarkers. We propose that future risk-assessment models use the design suggested in paper IV, Fig. 1. Genetic and lifestyle factors are already of importance early in life while comorbidity factors achieve increased importance with the greater age of the individual. We would like to emphasize that in current risk models for cancer, comorbidities are rarely, if ever, included.

Lung cancer and prostate cancer are important issues in terms of health care decisions. In the future, new treatments, especially new pharmacy, are to change the relationship between treatments, costs and survival. In future research this also needs to be considered, as costs of lung cancer are likely to increase. It is of importance also further examine in what way results are affected by the patient´s contacts with the health care system, the patient´s lifestyle and socioeconomic background or the health care system itself (organisation, competence etc). Our data was monitored for a population diagnosed in 2000-2005, giving a picture of costs before the new medical treatment options for prostate cancer was available in full clinical practice. For future studies this might serve as an important base for comparisons. Our data, therefore, provide a baseline for further studies of the effects of the new targeted therapy. One important question for the future is how to prioritize limited resources and how to move resources from treatment to prevention .

Patients' type of cancer and disease stage has an impact on partners' reaction and its consequences in terms of health care use and health care costs. Being a partner of a person with cancer means an increased risk in psychiatric morbidity. With an increase in cancer incidence, treatments with longer duration and a major part of cancer care are provided on an outpatient basis, which means that the demands and burden on the family of the cancer patient are likely to increase. Discussion is needed about the responsibility for the care of the partner—should oncology care also include the family? The emotional and physical well-being of the partner is of importance both from a medical point of view as well as of social perspective. Knowledge is also needed on how to support the partner in the most efficient way. When planning for care and allocation of resources for care the impact on the partner should also be considered.

Finally, the findings show that ordinary register-based data are valuable and ought to be better used in the management of the health care to support the clinicians in their work for best practice.

11 SWEDISH SUMMARY

Södra Regionvårdsnämnden har önskat att få belyst om vi har en rättvis och jämlik cancervård i Södra sjukvårdsregionen. Därför har en populationsbaserad registerstudie med många olika etapper genomförts. Basinformationen har hämtats från Tumörregistret i Södra sjukvårdsregionen. Första diagnosdatum noterades och hemort (kommun, distrikt, län) samt sjukhus definierades efter registreringarna vid detta första diagnosdatum. I inledande etapper användes data för åren 2000-2005 för patienter som diagnostiserats med de fem vanligaste cancerformerna: kolon-, rektal-, bröst-prostata- och lungcancer (ca 50 % av all cancer). I senare etapper breddades studien genom att ta med alla cancerformer och data avsåg då även åren 2006-2007.

Delstudierna har på olika sätt kompletterats med data från befolkningsregistret, olika patientregister, läkemedelsregistret (förmån, öppen vård), kvalitetsregister avseende prostata- respektive lungcancer, vård- och kostnadsdata i Region Skåne (sjukhusvård/offentlig primärvård/privat vård) och även försäkringskassans register över sjukdagar/-episoder (i tilläggsartiklar).

Studien har belyst insjuknande, omfattning och lokalisering av vård, överlevnad och kostnader för cancerpatienter/anhöriga i Södra sjukvårdsregionen. Analyser har gjorts avseende händelser som kan indikera bättre möjligheter till snabbare diagnos och lika behandling oavsett var man bor i regionen (har endast presenterats i en rapport). Särskilda kostnadsjämförelser har gjorts för de som har överlevt jämfört med de som avlidit. Analyser gjordes över samband mellan personers andra sjukdomar och den cancer man insjuknat i för att ta reda på om personer som var multisjuka (hade komorbiditet) hade större risk att insjukna i cancer. Vidare har kostnadsanalyser gjorts av olika behandlingar av prostata- och lungcancer. Överlevnad beräknades från diagnosdatum i dagar. Patientens hemort analyserades som bostadsort vid diagnos. Fördjupad analys över dödligheten har gjorts för patienter som insjuknat i lung cancer.

Säkerställda skillnader mellan olika befolkningsområden har påvisats för de fem stora cancerformerna avseende insjuknande, främst lungcancer och i överlevnad/dödlighet, främst avseende prostata- och lungcancer. Män hade klart lägre överlevnad än kvinnor vid kolon-, rektal- och lungcancer. I den utvidgade studien fanns på motsvarande sätt säkerställda skillnader mellan befolkningsområden i dödlighet även för bl a malignt lymfom och levercancer. Resultaten har redovisats i fyra olika rapporter.

Samband mellan 18 olika cancerformer och demens, diabetes, fetma och onormala blodfetter har analyserats. Diagnosen demens var klart lägre hos cancerpatienterna än hos kontrollgruppen. Säkerställda resultat var för sig uppnåddes för: koloncancer, prostatacancer, lungcancer, melanom och cancer i urinblåsan eller i urinvägarna. Sammantaget förekom demens i 40 procent lägre omfattning bland personerna med cancer. Ju längre in i kroppen tumörerna har suttit, desto lägre var förekomsten bland dementa. Detta tyder på att man inte tittar efter ordentligt hos patienterna med demens och för den gruppen bara diagnostiserar de tumörer som är lätta att upptäcka.

Samtidigt har de som har diabetes, fetma eller onormala blodfetter betydligt större risk att få olika former av cancer. För de senare sjukdomsgrupperna gjordes även både enkla och kombinerade analyser dvs de som hade diabetes jämfördes med kontroller samtidigt som de som hade t ex både diabetes och fetma också jämfördes med kontroller. De som insjuknar i diabetes visade sig ha en ökad risk att senare drabbas av bröstcancer samt cancer i lever, tjocktarm, bukspottkörtel och urinblåsa. Hos de som lider av fetma är det vanligare med cancer i livmodern, tjocktarm och njure samt för dem över 60 även bröstcancer.

För patienter med prostata fanns en stor skillnad mellan kostnader för överlevande och avlidna patienter. Sjukvårdskostnaderna steg med högre Gleason-score (sjukdomsgrad) året efter diagnostillfället. Högst sjukvårdkostnader konstaterades för patienter som fick strålbehandling. Lägst

kostnader hade patienterna som inte fick någon behandling. Patienter med kurativ behandling hade högre kostnader än de som fick palliativ behandling. Anhöriga ökade sin sjukvårdskonsumtion både det första och det andra året efter att patienten fått sin prostata-cancerdiagnos innebärande ökade sjukvårdskostnader.

Större delen av kostnaderna för patienter med lung cancer uppstår första året efter diagnos. Det fanns även här stor skillnad i kostnader för de som överlever och de som senare avlider. Patienter som opererats hade högre kostnader jämfört med de som endast fick cellgifter eller som strål-behandlades. Totalt sjönk kostnaden ju svårare sjuk patienten var.

En problematik vid kostnadsanalyser är att kostnader för läkemedel vid utprovning/test i särskilda studier och som då bekostas av läkemedelsföretag oftast inte finns med i redovisningen. När kostnaderna för olika behandlingar jämförs med överlevnadstiden för behandlingarna fanns en del svårförklarliga resultat som kräver ytterligare studier för man ska kunna dra några slutsatser.

Eftersom det hade påvisats stora skillnader i överlevnad/dödlighet för patienter med lungcancer i den inledande studien gjordes en analys för att undersöka hur olika faktorer påverkar utfallet. Hög dödlighet förklaras främst av att patienten inte fått någon behandling, har dåligt allmäntillstånd eller har insjuknat i ett avancerat sjukdomsstadium. De mest ”skyddande” faktorerna är om patienten blivit opererad eller haft kort remisstid från besök till behandling. Här visades också att befolkningen i de geografiska områden som i grundstudien hade högre dödlighet fortfarande hade detta även när hänsyn togs olika bakgrundsfaktorer.

För anhöriga visar resultatet en ökad vårdkonsumtion och ökade vårdkostnader tiden efter patientens cancerdiagnos hos framförallt anhöriga till patienter med koloncancer och lungcancer. Antalet sjukdomsdiagnoser ökade signifikant för hela anhöriggruppen med 24 % året efter den cancersjukes diagnos. Psykiatriska diagnoser ökade signifikant hos anhöriga till kolon-, lung- och prostatacancer.

Lungcancerpatienterna hade högst och patienterna med prostatacancer lägst antal sjukskrivnings-dagar. Patienter med anhöriga hade 48 % fler sjukskrivningsdagar än de som var utan anhörig. Anhöriga till lungcancersjuka hade störst antal sjukskrivningsepisoder och antal sjukdagar, och en jämförelse med normalbefolkningen visade att en signifikant ökning av sjukskrivning för denna grupp med 76 %. (Detta har redovisats i artiklar som inte ingår i avhandlingen).

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14 ORIGINAL ARTICLES