Chronic diseases and non-melanoma skin cancer

The impact on risk and prognosis

PhD thesis

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Preface

This PhD thesis was carried out during my employment at the Department of Dermatology and the Department of Clinical Epidemiology, Aarhus University Hospital.

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Content

Introduction

Non-melanoma skin cancer (NMSC)

The term non-melanoma skin cancer (NMSC) is commonly used to refer to basal cell carcinomas (BCC) and squamous cell carcinomas (SCC). It thus defines a population of cancer patients by what they do *not* have, which impedes proper study and demeans the significance of this ailment. Further, NMSC also encompasses other cutaneous malignancies, including cutaneous lymphoma, Merkel cell carcinoma, Paget's disease, angiosarcomas and malignant histiocytomas (1). This thesis is concerned with Bowen's Disease, basal cell carcinomas and squamous cell carcinomas. A better name for these cancers would be keratinocyte carcinomas, however since the term NMSC is used in the four studies, it will also be used throughout this thesis with the understanding that it refers to keratinocyte carcinomas only.

Basal cell carcinoma

Basal cell carcinoma was first described in 1903 (2). Tumour may originate from diverse sites and cells, but the most common opinion is that it arises from the basal cells in the epidermis. Metastasis of BCC is very rare (3, 4). Spread occurs most commonly via lymphatic paths to regional nodes and via the bloodstream to lungs and bones. The primary tumour of a metastatic BCC is found on the head and neck, is large and has been present for many years. Any subtype of BCC may give rise to metastases (1). Although BCC is rarely lethal, it is the most common cancer among the Caucasians (5) and therefore represents a significant health problem with regard to treatment and healthcare expenses.

Classification of BCC subtypes is made according to growth patterns, which may help the clinician in planning the optimal therapeutic procedure. However, the clinical categories are commonly used (as suggested by the WHO) and will be briefly presented below.

Noduloulcerative BCC

Sixty percent of BCCs are noduloulcerative (1), and this tumour type is commonly found on sun-exposed sites such as head and neck. The lesion is a red, well-defined nodule with a translucent appearance and overlying telangiectasia. Ulceration may occur, especially as the tumour grows. The growth pattern is circumscribed and with time, these tumours may reach a large size and extend

deeply. Cystic degeneration often occurs and for this reason the cystic variant of BCC is often taken as a noduloulcerative BCC (1).

Superficial BCC

This tumour is also common and its incidence is rapidly rising, especially among young people and more in women than in men (6-10). It is predominantly found on the trunk and extremities although head and neck may also be affected. *Multiple* lesions are common. The lesion is typically flat, pink or red, and there may be a translucent elevated border. The growth pattern is horizontally, which is the reason why this tumour can reach a very large size. Although metastases are rare recurrence after treatment is common (6).

Morpheaform BCC

This less common form of BCC is also the one with the most "malignant" potential (6). The lesion is indurated, sclerotic and ivory in colour, sometimes with overlying telangiectasia. The growth pattern is diffuse, the spread is subclinical; the margins are hard to determine, which is the reason for high recurrence rate after treatment of morpheaform BCC.

Bowen's Disease

Bowen's disease was first described in 1912 as a precancerous dermatosis (11). It is now known as an intraepidermal neoplasia of the skin and mainly regarded as a squamous cell carcinoma in situ. The neoplasia may clinically represent the transitional stage between an actinic keratosis and SCC. Bowen's disease manifests itself most frequently as a slightly scaly discrete erythematous plaque with a sharp but often irregular or undulating border. The surface may be hyperkeratotic, fissuring, dyspigmentated or ulcerative. Bowen's disease on sun-exposed areas is more common but less aggressive compared with those in sun-protected areas. Lesions grow in a progressive manner and may be single or multiple (1).

Squamous cell carcinoma

The cell of origin of this tumour is the epidermal keratinocyte which undergoes malignant transformation. Ninety-five percent of SCCs may be cured if treated early but a subset of tumours behaves aggressively, with high rates of recurrence and metastases. SCC metastasizes primarily through the lymphatics to regional nodes with the parotid and cervical nodes most commonly

involved. Distant visceral spread is rare without regional nodal involvement. Generally, primary tumours located at sun-exposed sites have the lowest risk of metastases. However, lip, ear and intraoral SCCs have a very high metastasis rate. SCCs have a rough, adherent scaly appearance and it grow both in width and depth. Advanced SCCs can be nodular and ulcerated. Pain, parastesthesias, dysesthesia and nerve paresis are common symptoms and indicate underlying spread (1).

Multiple carcinomas

Multiple carcinomas are defined as a new non-recurrent NMSC after the first NMSC. As the skin is the body's largest organ and mortality from NMSC is low, multiple carcinomas are commonly seen. A recent study found a 44% three-year risk of a BCC after a BCC and a 18% three-year risk of a SCC after a SCC (12). The three-year risk of a SCC after a BCC was 6%, whereas the three-year risk of a BCC after a SCC was 43% (12). General immunosuppression is a predisposing factor for multiple carcinomas of any type; therefore, multiple carcinomas are seen among transplant recipients, HIV patients and patients with leukaemia or lymphoma. In the otherwise healthy population superficial BCC accounts for the majority of multiple carcinomas (1).

NMSC incidence

The incidence of NMSC is rising worldwide with the highest increase reported in Australia, where fair-skinned people live in the closest proximity to the equator (5, 13). This accounts for both BCCs and SCCs, with an annual rate of increase in incidence as high as 3-10%. Reports from the Danish Cancer Registry show the same trend, although in Denmark the increase rate is more modest (figure 1).

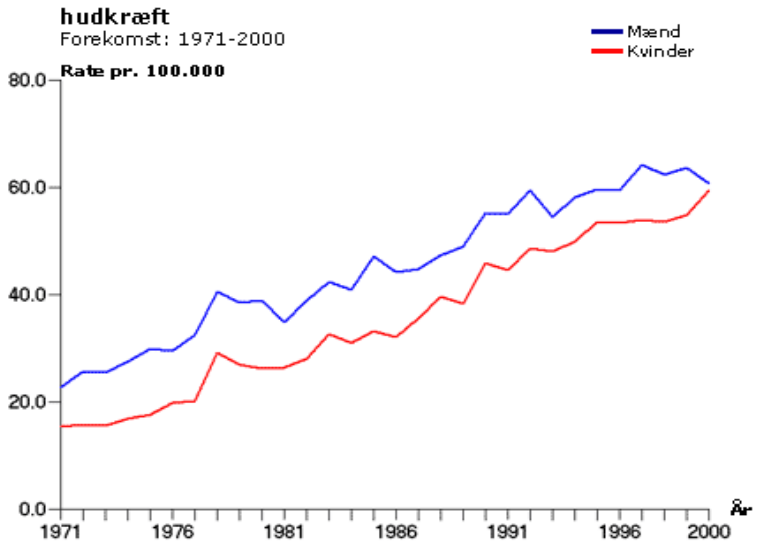

Figure 1. Incidence of NMSC among males (blue graph) and females (red graph) in Denmark from 1971-2000 (14).

Generally, the ratio of BCC:SCC is 4:1. The ratio depends on latitude and is, notably, reduced in Australia and increased in Denmark where the ratio of BCC:SCC is 9:1.

The male: female ratio is 1:1 among BCC patients world wide. SCC affects men 2-3 times more often than women, which can be explained by men having more frequently outdoor occupations, less protective clothing and therefore a greater lifetime cumulative UV-light exposure (13). This distribution may change in the future since SCC incidence increases more rapidly among women (15).

Risk factors for NMSC

Multiple and related risk factors are associated with the NMSC development (1). Both genetic and environmental causes are involved in the multistage process of carcinogenesis, including tumour initiation, promotion, premalignant progression and malignant conversion of normal skin cells into cancerous skin lesions (1).

Ultraviolet radiation, skin phenotype and the latency and dosage effect

Sunlight is the single most important exogenous cause of NMSC (16). Ultraviolet-B (UVB), UVA and UVC rays can induce DNA damage in normal skin cells. While most studies show that the primary part of the solar spectrum responsible for development of these cancers is UVB, UVA is also carcinogenic (16). UVC is absorbed by the ozone layer and does not reach the earth's surface.

UVB causes mutations and immunosuppression essential to photo-carcinogenesis, with effects primarily limited to the epidermis. UVA makes up to 90-95% of the ultraviolet radiation reaching the human skin, and it affects both the dermis and epidermis by producing genomic instability.

Just as important as ultraviolet light is the skin phenotype and its reaction to sunlight. Fitzpatrick skin types I and II (fair and/or easily sunburned) are known to confer increased risk of both BCC and SCC; having such skin type is also an independent prognostic risk factor. However, after accounting for other phenotype variables the tendency of propensity to burn rather than tan upon sun exposure ceases to be a prognostic factor (1).

Latency[1], timing and dosage of UV exposure are also important regarding risk of BCC and SCC. The latency between UV exposure and development of BCC is long since it is the early life (and intermittent) exposure that appear to predispose to BCC (5, 17), whereas it is the recent and cumulative sun exposure that appear to predispose to SCC (18). The same effect of latency and dosage has been found among patients treated with PUVA (i.e., psoralen and ultraviolet-A light), whereby exposure to PUVA is associated with a persistent, dose-related increase in risk of SCC but has a much weaker effect on the risk of BCC (19).

Chemicals and smoking

Exposure to ionizing radiation, either iatrogenic (treatment for acne, tinea capitis, cancer), or occupational (uranium in mines) or accidentally (atomic bomb explosion), elevates the risk for BCC 3-fold (20). An elevated risk for SCC has also been found but only in individuals prone to sunburn with sun exposure (21).

Among occupational exposures, polycyclic aromatic hydrocarbons, including mineral oil, shale oil, coal tar, soot and pitch, have been shown to elevate the NMSC risk, especially that of SCC (5, 22). Exposure to arsenic is a well defined cause of Bowen's disease, SCC and superficial BCC. This association has been found among industrial and agricultural workers who were exposed occupationally. In addition, arsenic oxide has been formerly used for treatment of psoriasis, eczema and asthmatic bronchitis, and subsequent cancers have been found among patients thus treated.

[1] Latency here refers to time between carcinogenic exposure and development of the tumour. It must be distinguished from the epidemiological term, latent period, which is the period between the onset of a disease and its diagnosis.

Evidence of these cancers among members of the general population exposed to arsenic through contaminated drinking water has also been shown (23).

Smoking has been reported to double the risk of SCC with a clear dose-response relation (24). However, no clear relation has been found between smoking and risk of BCC.

Aging

There is a clear relation between the function of the immune system, aging and the incidence of NMSC. This suggests that the "immuno senescence" weakens cellular immunity, inhibiting surveillance of the malignant transformation of normal cells (25-28). Alternatively, age effect may reflect the elapse of a sufficient period of time from carcinogenic exposure of UV light and/or the accumulation of the dosage needed for these cancers to develop. Finally, a weakened immune system and a sufficient carcinogenic exposure from UV light may act in concert to produce cancer. Regardless of the underlying mechanism, an incidence of NMSC increases with age, and it does so markedly after the age of 40 (10, 29). Therefore, because of longer life expectancy among both women and men, an overall further increase of NMSC incidence can be expected.

Prognosis of NMSC

Several factors influence the outcome of a disease (figure 2). The simplest way to assess health outcome in a particular population, here in the population of NMSC patients, is by estimating associated morbidity (diseases) and mortality (deaths). More complex health indicators are discomfort, disability and dissatisfaction (quality of life) (30).

Mortality from BCC is very low and, according to reports, it further declined in the period from 1980 to 2000 (31). Mortality from SCC is approximately 12 times higher than that from BCC. In Denmark, the annual reported mortality rate is 0.4 pr. 100,000 for NMSC but inaccuracies in death certificate information may cause overestimation of the actual mortality (29, 32, 33).

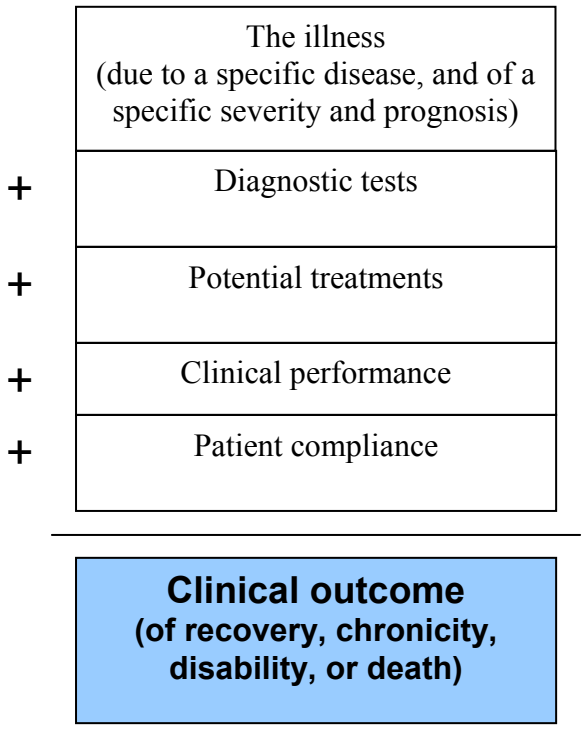

Figure 2. Factors influencing the outcome of a disease (34). This model applies to an outcome-oriented review of the performance with a specific disease. The model is not suitable when adverse outcomes of dangerous clinical actions are rare, when adverse outcomes of bad performance are delayed or when unfavourable outcomes are the result of factors beyond the clinician's control.

According to figure 2, prognostic factors for NMSC can be divided into NMSC-related factors, diagnosis, treatments, clinical performance of the treating clinician treating, and patient factors. The patient factors include diagnostic proposal, acceptance of the treatment plan, compliance and physical performance (associated chronic comorbidities and lifestyle).

NMSC-related factors cover type of NMSC and the risk profile of the tumour. For SCC, a higher mortality is seen among patients with tumours located on lips and ears, and in anogenital areas (29). Other high-risk precursors are large tumour size (>2 cm), poor to moderate differentiation, and deep invasion (1). High-risk SCC is therefore defined as a tumour larger than 2 cm, poorly or moderately differentiated and with perineural invasion (1). For BCC, aggressiveness of the tumour is also dependent on location, with tumours of head and neck (especially those located on the ear and the eyelid) more commonly metastatic (29). Other high-risk precursors of BCC are tumour size (>2 cm) and histological subtype, with morpheaform BCC being more malignant than noduloulcerative and

superficial BCC) (1). Besides, BCCs accompanied by squamous metaplasia are aggressive and may be lethal (1).

In managing patients with NMSC, the *treatment factor* should be kept in mind; it may be modified by the performance of the clinician treating the NMSC and by the patient's acceptance of the treatment plan. The most important factor is total removal of the tumour. Because these tumours are considered less serious than some others due to their slow growth and low metastasis rate, an optimal cosmetic result often receives a higher priority than total removal. The consequences of that are increased morbidity and, in worst cases, mortality (29, 35).

Among *patient factors* that affect NMSC prognosis are general demographic characteristics, such as age, gender and race. Higher NMSC-related mortality is seen with increasing age, male gender, and in the white population (29). The patient's physical performance, especially the immune status prior to the diagnosis of NMSC, is important. Chronic comorbidities are known to have an impact on prognosis of most diseases (36), and it is well known that NMSC, particularly SCC, is extremely aggressive, accounting for the vast majority of deaths among organ transplant recipients (37). The patient's lifestyle is likewise important: avoiding tobacco and alcohol may improve the patient's physical performance and thereby the outcome of NMSC. The individual patient's compliance according to diagnosis is also essential. Some patients may ignore having a slow growing tumour, resulting in delayed diagnosis, in turn associated with worse prognosis. Physicians may likewise ignore NMSC in patients with severe comorbidities because of the perceived triviality of this cancer compared with coexistent severe medical conditions. A delayed diagnosis and a worse prognosis are potential consequences of such perception.

Chronic diseases and the impact on risk and prognosis of NMSC

An increased risk of NMSC has been observed among patients having certain chronic diseases (38-42). Potentially there are four ways by which presence of chronic diseases can modify risk and prognosis of NMSC. These are similar to the abovementioned prognostic factors influencing the outcome of NMSC:

1) The *treatment factor*. Medications used to treat a chronic disease may increase the risk of NMSC, as for example, with treatments for solid cancers (15, 43-47), psoriasis (48), atopic dermatitis (38), rheumatologic diseases (39) and organ transplants (49-51).
2) The *chronic disease* itself. Diseases associated with a weakened immune system, i.e. leukaemia and lymphoma (52) or acquired immunodeficiency syndrome (AIDS) (53, 54) are known to substantially increase risk of NMSC.
3) A combination of the chronic disease and the medications used to treat the disease.
4) The *diagnosis* of the chronic disease and the *clinical performance* of the clinician treating the chronic disease.
5) The *patient factor*, such as a certain lifestyle associated with both having a chronic disease and developing a NMSC.

Immunosuppression and Human Papilloma Virus (HPV) as a model for how chronic diseases may modify risk and prognosis of NMSC

General immunosuppression is a major risk factor for both BCC and SCC. Transplant patients have a 65-fold increased risk of SCC (55), and among heart transplant recipients surviving beyond the 4th year, NMSC and in particular SCC are extremely aggressive (37). The risk of developing skin cancer in transplant patients may depend on the level of immunosuppression and type of treatment (56-58). A reduction of dose or an elimination of some immunosuppression will reduce the tumor burden (54, 57-60), indicating a dose-response relation.

Infection with certain types of human papilloma virus (HPV) is known to increase risk of SCC (but not BCC), although the oncogenic mechanism remains uncertain. It has been suggested that the HPV infection modifies the risk of UV-light induced skin cancer (61). The evidence for involvement of specific HPV types in SCC originated from studies of patients suffering from the rare Epidermodysplasia Verruciformis (EV) and organ transplant recipients (5). Immunosuppression appears to allow the virus to proliferate, however, epidemiologic studies of HPV as a risk factor for SCC in otherwise healthy individuals are more sparse and evidence is less convincing (62-65).

Methodological problems in studying NMSC

Observational studies are suitable for studying risk factors and prognosis of NMSC. When conducted properly, they can supply important knowledge about the disease. Observational studies that draw study population from prospective administrative databases have a number of advantages, namely: 1) timely and early dissemination of information on outcome of NMSC; 2) large study sizes, insuring high precision of risk estimates while warranting generalization; 3) low cost due to using data that are already collected; 4) data collection is prospective and is uncoupled from the objective in the study of interest. Knowledge about risk and prognosis of NMSC drawn from such studies carries benefits for clinicians, patients, and the general population.

Nevertheless, it is important to understand limitations of administrative databases in studying NMSC. Worldwide, data on NMSC are not routinely collected by many cancer registries; in some registries only SCCs are recorded while in others BCCs and SCCs are recorded as one entity (66). Likewise, in the Danish Cancer Registry, registration of NMSC is incomplete (43, 44, 48, 67-69). Reasons for the incomplete registration include: 1) under-reporting due to high cure rate (leading clinicians to regard these skin cancers as trivial); 2) large number of these cancers threaten to overwhelm surveillance systems; 3) difficulties in ascertaining cases, because multiple lesions are often diagnosed simultaneously or because many people have multiple lesions in their lifetime (13, 70). The problems arise when registered and unregistered NMSC patients differ according to risk factors and outcome variables. Such differential data completeness will lead to *bias* in the estimates of effects.

Selection bias

Selection bias arises when the association between exposure and outcome differs between participants and non-participants of a study (71). In cohort studies selection bias can arise if the prognosis among participants of the study differs systematically from the prognosis of non-participants of the study or due the non-random loss to follow-up. In a case-control study, selection bias arises if case status is misclassified, or if the association between the exposure risk factor and risk of NMSC differs systematically between participants and non-participants of the study.

Information bias

Errors in data collected on study subjects cause information bias (71). Such errors include misclassification of exposure, outcome, or confounding factors. Systematic errors arise if rates of misclassification are differential among comparison groups; as a result, effects can be either under- or overestimated (72). Again, because of the low completeness of NMSC registration, information bias is likely to occur due to lack of differentiation between first primaries and new subsequent cases. This may cause bias in a cohort study of prognosis because patients with new subsequent disease are better survivors (30). In a case-control study information bias may arise from differential surveillance among the exposed having the risk factor under study and the unexposed not having the risk factor. If the exposed receive less or more medical attention, they may have a lesser or greater likelihood to have a NMSC detected, respectively. This, again, could either under- or overestimate the risk estimates.

Confounding

Confounding means "mixing of effects" and implies that the effect of the study exposure is mixed with - or masked by - the effect of an extraneous variable, leading to bias (71). Confounding arises from imbalanced distribution across exposure categories of risk markers and prognostic factors for the outcome. In studies of NMSC prognosis, the effect of the factor under study (e.g., comorbidity) could possibly be mixed with or masked by an effect of another factor or trait (e.g., age, gender, or social economic position). To act as a confounder in a study of NMSC prognosis, a factor must 1) itself be a risk factor for the outcome (e.g., death), 2) be unevenly distributed between persons with and without NMSC, and 3) not be a consequence of having an NMSC.

Chronic diseases and risk of NMSC

Little is known about the overall impact of chronic diseases on the risk of developing NMSC. If an association is suggested, it is not clear whether it is due to the chronic disease itself or to medications used to treat it. We searched the electronic database MEDLINE (from 1966 to July, 2007) using the terms "chronic disease" or "comorbidity" or "chronic morbidity", "skin cancer NOT malignant melanoma" and "epidemiology". This search strategy yielded 176 studies. In addition we searched EMBASE (from 1980 to July, 2007) using the terms "basal cell carcinoma" or "squamous cell carcinoma AND skin cancer" or "nonmelanoma" and "comorbidity", a strategy that

yielded 30 studies. None of the studies examined the overall impact of chronic diseases on NMSC risk (as was done in study III of this thesis) and were therefore not relevant for this thesis.

We then wished to evaluate certain chronic diseases with respect to their impact on the risk of NMSC, with special focus on separating the treatment factor from the disease factor and the methodological problems arising in epidemiological studies of NMSC risk factors. We searched the electronic databases for studies of distinct chronic diseases as risk factors for NMSC. We used the terms “rheumatoid arthritis”, “psoriasis”, “atopic dermatitis”, “solid cancers” in addition to “skin cancer NOT malignant melanoma” and “epidemiology”. This search strategy yielded 172 studies. Only observational studies and those that were published as full-length articles in English were considered; reviews were excluded. Further, we excluded studies describing the cancer incidence among transplant recipients, studies of treatments already known to increase risk of NMSC (such as UV-light therapy and radiotherapy), and studies describing risk of NMSC other than BCC and SCC. Six studies satisfying these criteria are summarized in table I.

E. F. Chakravarty *et al.* (40) reported an increased risk of NMSC among rheumatoid arthritis (RA) patients taking prednisone and TNF inhibitors in combination with methotrexate, when compared with RA patients not taking these medications. This result suggests that NMSC risk is related to medications used to treat RA rather than RA itself. C. F. Paul *et al.* (41) showed an increased risk of NMSC among psoriasis patients treated with cyclosporine longer than 2 years compared with those thus treated for less than 2 years. In addition, they found an effect of PUVA, retinoids and methotrexate treatment. None of the above analyses included adjustment for disease severity (confounding by indication). M. E. Ming *et al.* (73) adjusted for treatment while examining the risk of NMSC in patients with atopic dermatitis (AD) and found no overall change in the risk. However, no association was observed even in the absence of adjustment for treatment of AD which may be an artefact of selecting both cases and controls among dermatological patients. Lack of an association between dermatological diseases and the risk of NMSC may result from increased surveillance for skin cancers in these settings. L. Richiardi *et al.* (42), studying risk of cancers following testicular cancer used histology as a proxy for treatment, thereby separating the chemotherapy effect (nonseminomas) from the irradiation effect (seminomas) on cancer risk. Risk estimates for NMSC was similarly elevated among both seminoma and nonseminoma patients, indicating a similar effect – of either testicular cancer or therapies for it – on the NMSC risk.

The abovementioned positive associations between the certain chronic diseases and NMSC must be interpreted with caution, since none of these studies examined potential impact of patient selection bias or surveillance bias on the results (study III).

Chronic diseases and mortality of NMSC

It is well known that, compared with other malignancies, the prognosis of NMSC is favourable. However, little is known about the prognosis after NMSC compared with the general population. A way to assess relative mortality of NMSC patients compared with the general population would be to estimate the mortality rate ratio or the standardised mortality ratio. Besides, since NMSC generally affects older people, and older people bear the disproportionate share of the chronic disease burden, it is important to know how chronic diseases influence the NMSC prognosis. In addition, any association between NMSC and cause-specific mortality will provide further insight into the disease's clinical course and foster our understanding of NMSC and its underlying aetiology.

We aimed to evaluate mortality of NMSC patients, as compared with the general population, with special focus on addressing methodological issues expected when conducting epidemiological studies of NMSC prognosis. We searched the electronic databases MEDLINE (from 1966 to July, 2007) and EMBASE (from 1980 to July, 2007) using the terms "Nonmelanoma skin cancer" and "mortality" or "cause-specific mortality", and "basal cell carcinoma" or "squamous cell carcinoma AND skin cancer" or "nonmelanoma" and "comorbidity". This search strategy yielded 138 studies. We further searched for "Nonmelanoma skin cancer" and "prognosis". This search strategy yielded 70 studies, mainly covering treatment effects and quality-of-life assessment. We only included studies describing relative mortality of NMSC patients compared with the general population; studies evaluating causes of death among NMSC patients; or studies examining the influence of comorbidity on mortality. Further, only those that were published as full-length articles in English were considered, while reviews were excluded. Thereby, four studies remained and these are shown in table II.

M. A. Weinstock *et al.* using data from death certificates, found a high degree of misclassification on the causes of death from skin cancer among NMSC patients. This misclassification produced an

overestimation of the mortality rate from these cancers (29, 31, 32, 74). S. Karjalainen *et al.* in their study in Finland, found no increased mortality among BCC patients and a slightly elevated mortality among SCC patients, compared with the general population (75). H. S. Kahn *et al.* in the United States, reported no difference in overall mortality of NMSC patients compared with the general population and a reduced mortality from circulatory diseases (76). However, they did not stratify NMSC by type (BCC or SCC). A. J. Charles *et al.* evaluated comorbidity (measured by the Charlson Comorbidity Index) and its effect on NMSC mortality (77); the relative mortality was measured by comparison with the expected mortality in the US Standard Population, which precluded proper adjustment for comorbidity. Neither comorbidity nor the underlying type of NMSC has been well examined regarding relative mortality of NMSC (study I and Ia), while patterns of cause-specific mortality among NMSC patients from causes other than skin cancer are still unknown (study I and IV).

Table I: Studies of chronic diseases as risk factors for non-melanoma skin cancer (NMSC)

Authors	Country	Study period	Design	Number	Exposure assessment	Risk estimates	Adjustments	Results
L. Mellemkjær *et al.* (39)	Denmark	1977-1987	Cohort	20699 patients with rheumatoid arthritis	Rheumatoid arthritis recorded in the Danish Hospital Discharge Registry	RR, the ratio of observed-to-expected number of cancers	Age and gender and calendar period.	A RR of 1.4 (95% CI: 1.1-1.9) for SCC and 1.3 (95% CI: 1.1-1.4) for BCC
E. F. Chakravarty *et al.* (40)	USA	1999-2003	Cohort	15789 patients with rheumatoid arthritis	Rheumatoid arthritis patients participating in the National Data Bank for Rheumatic Diseases (diagnosis made by rheumatologists)	Hazard ratio, as an estimate of incidence rate ratio.	Age, gender, race, marital status, a history of prior NMSC. Stratification on treatment	Increased risk of NMSC among RA (HR = 1.19, p=0.042), further associated with prednisone and TNF inhibitor use.
C. F. Paul *et al.* (41)	Multicenter (Europe and Canada)	?	Cohort	1252 patients receiving cyclosporine for psoriasis	Psoriasis patients treated in one of the participating dermatology centres.	Standardised incidence ratios (SIR)	Age and gender and calendar period. Stratification on treatment type and intensity.	SIR of 1.8 (95% CI: 0.6-4.1) for BCC and SIR of 24.6 (95% CI: 13.8-40.7) for SCC.
A. B. Olesen *et al.* (38)	Denmark	1977-1996	Cohort	6275 patients with atopic dermatitis	Atopic dermatitis recorded in the Danish Hospital Discharge Registry	Standardised morbidity ratios (SMR)	Age and gender and calendar period.	SMR of 2.4 (95% CI: 1.4-3.9) for keratinocyte carcinomas.
M. E. Ming *et al.* (73)	USA	1998-2001	Case-control	1533 cases with NMSC	Atopic dermatitis and other skin diseases, self-administered questionnaire	Crude and adjusted odds ratios	Age, gender, topical steroid use and ethnicity.	Adjusted OR of 0.78 (95% CI: 0.61-0.98) for NMSC.
L. Richiardi *et al.* (42)	Europe, Canada and Australia	1943-2000	Cohort	29511 patients with a primary testicular cancer	13 population-based cancer registries	Standardised incidence ratios (SIR)	Age and gender and calendar period. Stratification on histology.	SIR of 3.19 (95% CI: 2.02-4.79) for NMSC after 20 years of follow up after testicular cancer.

Table II: Studies of chronic diseases as prognostic factors for non-melanoma skin cancer (NMSC) mortality

Authors	Country	Study period	Design	Number	Outcome assessment	Risk estimates	Adjustments	Results
S. Karjalainen *et al.* (75)	Finland	1967-1982	Cohort	23975 patients with BCC and 2927 patients with SCC	Total death through the Central Statistical Office of Finland (complete follow up).	Standardised mortality ratios (SMR) as an estimate of relative survival rate (RSR).	Age, gender and calendar period	10-year RSR of 98.8 for male BCC patients and 100.3 for female BCC patients. A 10-year RSR of 87.2 (Standard Error (SE) 4.4) for male SCC patients and 83.3 (SE 4.0) for female SCC patients.
M. A. Weinstock *et al.* (29) - and 3 other similar studies (31, 32, 74).	USA (Rhode Island state)	1979-1987	Case study	116 death, classified as NMSC	Cause-specific death from NMSC recorded by the Rhode Island department of Health, confirmed in the medical record	Mortality rate of NMSC according to histological subtype, age, gender and year of death	Age, gender and calendar period (1970 US Standard population)	Mortality rate of SCC on 0.33 pr. 100000 person years (py) and of BCC on 0.12 pr. 100000 py. A substantial misclassification of NMSC cause of death.
H. S. Kahn *et al.* (76)	USA and Puerto Rico	1982-1995	Cohort	35062 persons with NMSC	Total death through the National Death Index (93 % complete follow up) and cause specific death obtained from Death certificates.	Hazard ratio as an estimate of RR of total and cause-specific mortality from cancer, circulatory diseases and all other causes.	Age, race, educational level smoking, BMI, alcohol, exercise and age at treatment.	Total mortality of 1.03 (95% CI: 1.00-1.06) for male and 1.04 (95% CI: 1.00-1.09) for female NMSC patients. Cancer-specific mortality was increased and mortality from circulatory diseases reduced.
A. J. Charles *et al.* (77)	USA	1985-1994	Cohort	99 persons with NMSC who had Mohs micrographic surgery	Total death through the National Death Index; date of death obtained from death certificates and medical records.	Survival rate calculated with Kaplan-Meier life table method and Standardised mortality ratios (SMR) as an estimate of relative survival rate (RSR)	Age, gender and calendar period. Stratification according to Charlson Comorbidity Index(CCI).	Generally, a better survival than expected among NMSC patients with no comorbidities (p=0.008), the same survival compared with expected among NMSC patients with CCI 1-2, and a poorer survival among NMSC patients with CCI 3-5. Survival differed according to comorbidity index and the CCI is a valid prognostic instrument in predicting life expectancy among NMSC patients.

Conclusions

Prospective or administrative databases of NMSC are potentially important sources for studying risk factors and prognosis of NMSC. Keeping in mind the methodological problems of underreporting and incomplete registration of these cancers, proper research can be done. Although these tumours largely are attributable to factors relating to UV-light exposure and skin sensitivity to UV-light, studies reported an increased risk of NMSC in patients with certain chronic diseases (see table I). These studies generally focused on single diseases as risk factors for NMSC, without evaluating important biases associated with observational study design. The overall impact of chronic diseases on NMSC risk remains unknown.

It is well known that mortality rate from NMSC is low; consequently, this cancer may be regarded as trivial among some patients. However, being the most common of all cancers among the Caucasians, NMSC represents a significant health problem with regard to treatment and healthcare expenses. Several factors may influence the outcome of this disease; however it is generally unclear what impact the individual factors (i.e., NMSC related factors, treatment factors or patient factors) have on NMSC mortality. The presence of a chronic disease may influence the outcome of NMSC, and since NMSC primarily affects the elderly persons who also carry the largest chronic disease burden, it is of common interest to know how chronic diseases are associated with NMSC and influences its prognosis. This has only been superficially examined and therefore, the impact of chronic diseases on NMSC mortality remains unknown. In addition, the cause-specific mortality among the NMSC patients from causes other than skin cancer is unknown, while such information may contribute to a better understanding of the clinical course of NMSC.

Aims of the thesis

a. To compare the total and cause-specific mortality of NMSC patients with that of the general Danish population according to the histological diagnosis, anatomic distribution and the number of NMSC in the individual, while considering potential confounding by co-morbidity and civil status (study I). Further aim was to evaluate the strength of the relation between NMSC and mortality according to age, gender and level of comorbidity (effect modification) (study Ia).

b. To examine whether the finding of a reduced mortality among BCC patients could be explained either by differences in mortality among patients with first primary and new subsequent cases or with differences in mortality among patients registered in different data repositories (study II).

c. To evaluate any association between NMSC and chronic diseases overall and examine whether a history of previous hospitalization for selected chronic diseases was a risk factor for a subsequent diagnosis of NMSC. Additionally, we aimed to rule out the effect of surveillance and selection bias on the results (study III).

d. To examine total and cause-specific mortality of all NMSC patients registered in the Danish Cancer Registry during a 23-year period compared with that of the general Danish population. Additionally, we aimed to evaluate the effect of surveillance and selection bias, and unmeasured confounding on the results (study IV).

Subjects and methods

Data sources

This thesis is comprised of cohort (study I, Ia, II, IV) and case-control (study III) studies conducted nationwide in Denmark. The studies are mainly based on a nationwide cohort of NMSC patients assembled prospectively in 1995 (study I-III). The cohort was assembled in order to determine the disease profile and the true disease burden (incidence) of NMSC; the task was undertaken because of incomplete registration of these cancers to the Danish Cancer Registry. The study was initiated and conducted by the late Professor Gerda Frentz who tragically died shortly after finishing the data collection. For this reason, the collected data have not been analyzed until 2005, when the work on this thesis started. Study IV is based on data on NMSC patients registered in the Danish Cancer Registry from 1978 to 2001.

Below is a detailed description of the data sources used in this thesis.

The Gerda Frentz cohort

In 1995, Professor Gerda Frentz established a nationwide cohort (the Gerda Frentz Cohort (GFC)) by prospectively recording all patients with NMSC seen by Danish dermatologists in 1995; both first primaries and subsequent new primaries were included. Two sources were used to establish the cohort. The first source was patients seen at private or public outpatient dermatology clinics, for whom the following clinical data were available: tumour site, size and clinical diagnosis, availability of the histological review of a biopsy (yes/no), treatment type, and history of an NMSCs. The second source comprised all patients with a histological review of suspected NMSCs sent from any other non-dermatology practitioner to a pathologist. These data also included biopsies diagnosed as NMSC, irrespective of the clinical diagnosis. Histological data on these tumors included the final histological diagnosis, the type of referring clinic and, if appropriate, details on the tumour's growth pattern, differentiation and excision borders.

The Danish Cancer Registry

The Danish Cancer Registry (DCR) has recorded primary cases of cancer on a nationwide basis since 1943 and has been shown to be accurate and to have a nearly complete ascertainment of cancer cases (78). The files of the DCR provide information on cancer type, site, morphology and

history of cancer. Tumours in the Cancer Registry are coded according to the 7th revision of the *International Classification of Diseases* (ICD-7) and, in addition, since 1978 according to the first version of the *International Classification of Diseases for Oncology* (ICD-O-1), which includes a four-digit code for tumour morphology (79). If a person develops more than one primary tumour, generally each tumour is registered and counted as an individual record; however, multiple tumours of the skin with identical morphologic characteristics (i.e., the same first 3 digits of the ICD-O-1 morphology code) are recorded only once, even when they are located on different parts of the body. Such tumours are, however, given a specific code for multiple occurrences.

The Danish Causes of Death Register

Causes of death were retrieved from the Danish Causes of Death Register (80) containing data on all deaths occurring among residents of Denmark since 1943. For patients who died before the end of 2001, the registry data had been computerized; for patients who died during 2002-2004, the causes of death data were not yet computerized, and we therefore manually extracted this information from the paper death certificates. For study I, we used the underlying cause of death reported on the death certificate grouped, as defined by the National Board of Health (80), into 22 categories based on ICD-10 codes, while for study IV, there were 49 standard categories based on ICD-8 and ICD-10 codes (80).

The Danish National Patient Registry

The Danish National Patient Registry stores data on 99.4% of all discharges from Danish somatic hospitals nationwide since 1977 (81). Since 1995, data on outpatients have also been included. For study I, Ia and III, we retrieved all discharge diagnoses (inpatient and outpatient whenever available) recorded since January 1, 1977 (the date the registry was established). Diagnoses were coded in ICD-8 system through 1993 and in the ICD-10 system thereafter (ICD-9 was never implemented in Denmark). In study I, we used data from the Danish National Patient Registry to compute the Charlson Comorbidity Index (CCI) (36) and adjusted for this variable in the analysis. In study Ia, we carried out analyses stratified according to the level of comorbidity based on the Charlson Comorbidity Index. In study III, the discharge diagnoses from the Danish National Patient Registry were used as the exposure variables.

The Danish Civil Registration System

In order to link data from different registries and to draw population controls (study I-III), we used a unique 10-digit civil registration number which is assigned to all Danish residents by the Danish Civil Registration System (82). From the Civil Registration System, we also obtained information on vital status (dead or alive), date of death, civil status and the area of residence of the study population members in studies I, Ia and II.

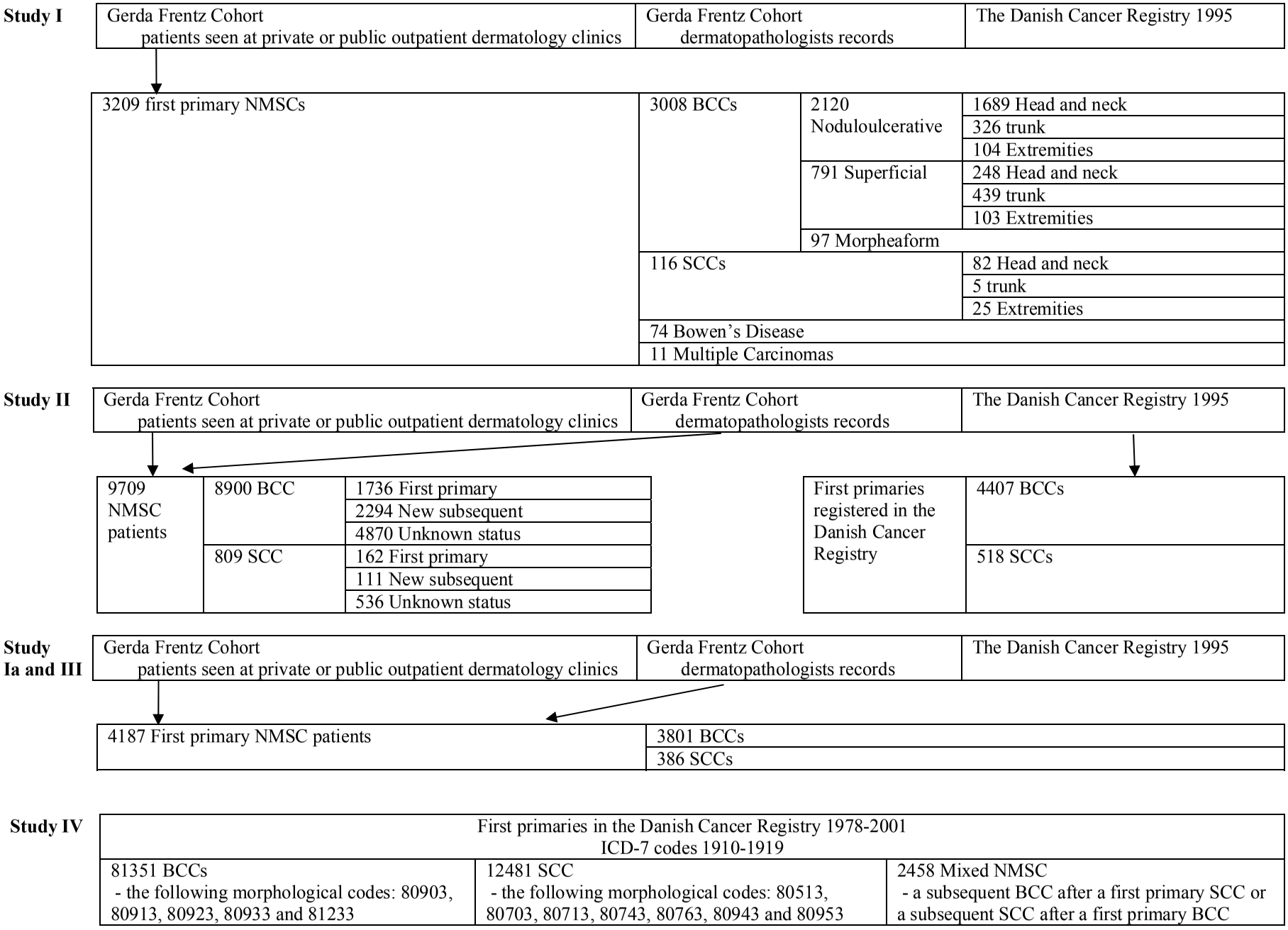

Figure 3. Source population in study I-IV.

Study designs

Cohort studies

The term cohort is used to describe a group of people with a common characteristic or trait. Upon entry in the study, the members of a cohort are classified as *exposed* or *unexposed*, according to presence or absence among them of a risk or prognostic factor under study which might be related to the study outcome. The outcome of interest is occurrence among the cohort members of a particular health-relevant event, such as death or onset of a disease. Studies I, Ia, II and IV of this thesis are cohort studies, with the outcome of interest being total and cause-specific mortality (Study I and IV), whose association with study exposures is expressed in terms of mortality rate ratio (MRR) and standardised mortality ratio (SMR). In study I, the exposed group (source population) consisted of patients with a first primary NMSC seen at private or public outpatient dermatology clinics (the first source of the Gerda Frentz cohort). These were further classified into subcohorts based on tumours' histological subtypes and locations. In study II, the exposed group was the entire source population from the Gerda Frentz Cohort, further subdivided into subcohorts of patients with BCC, SCC, first primary, new subsequent cases or patients with an unknown history of NMSC. In addition, first primaries registered in the Danish Cancer Registry in 1995 were a subcohort in study II. In study IV, first-primary NMSC patients registered in DCR during 1978-2001 comprised the exposed group and were further subdivided into groups with BCC, SCC or mixed NMSC. The unexposed (control) cohort was a group of persons obtained by sampling the general population. For study I, Ia and II approximately ten age-, gender- and residence-matched persons were drawn for each NMSC patient. In study IV, we calculated the SMR, and the information of mortality rates in the general population was based on age- and gender specific rates standardised to the Danish population. For further details, see figure 3.

Case control studies

The case-control study aims at achieving the same goals (e.g., measuring an association between an exposure and outcome) as a cohort study. Case-control studies are best understood by considering a source population, representing a hypothetical study population in which a cohort study might have been conducted. However, because the underlying cohort is sampled rather than followed in its entity, a case control study can be conducted more efficient. The study sample is assembled by first ascertaining patients who experienced the study outcome – *cases* (which are the same cases one would observe in a hypothetical cohort study), but instead of evaluating exposure status of the entire

cohort, it is estimated from a sample of that cohort – *controls*. Both *cases* and *controls* are then classified as being *exposed* or *unexposed* with respect to the *exposure* of interest. The distribution of exposure among cases is compared with that among the controls, whereby inferences can be made about the association between the exposure and the risk of the outcome. Because the purpose of the control group is to provide an estimate of the relative size of the exposed and unexposed components of the source population, it is important that the controls are sampled independently of exposure status. Study III of this thesis was a case-control study. Patients with first primary NMSC tumours in the Gerda Frentz cohort comprised the cases; the tumours were subdivided into BCC or SCCs. Using risk-set sampling (71), controls were drawn from the general population by linkage to the Danish Civil Registration System (i.e. the controls had to be alive and at risk for a first NMSC at the time the corresponding case was diagnosed in 1995 (the index date assigned to controls)). The controls were individually matched to cases on age, gender and area of residence. Hospitalization with selected chronic diseases was ascertained from the date of NMSC diagnosis, or index date of controls, until January 1, 1977 based on hospital discharge diagnoses recorded in the Danish National Patient Registry. For further details, see figure 3.

Confounding

In study I, we considered comorbidity level as a confounding factor, measured based on hospital discharge diagnoses. We computed the Charlson Comorbidity Index (CCI) (36), which is an extensively studied and validated instrument used to predict mortality (83). The index includes 19 major chronic disease categories weighed based on the associated relative risk of dying. The weights were derived in a cohort of American patients and the index was subsequently tested for its ability to predict risk of death from comorbid diseases in a second cohort of 685 patients during a 10 year follow-up (36). We used the CCI to define three levels of the comorbidity: 0 (“low”) for persons with no underlying diseases listed in the CCI; 1-2 (“medium”); and >2 (“high”), according to the disease categories of the original Charlson Comorbidity Index (36). In addition, we considered socio-economic position as a potential confounding factor. As a proxy for this, we used three levels for civil status on the index date; married, not married, or unknown, obtained from the Danish Civil Registration System. Age, gender and area of residence were balanced out in all studies by matching and could therefore not confound the associations.

Effect modification

When the strength of the association between the exposure and the outcome of a study differs according to the level of some third variable, the third variable is said to be an effect modifier. If anchored in a biologically plausible mechanism, the effect modifier's status as a confounder is of secondary importance since the estimate of the effect between exposure and outcome is different in patient populations defined by the stratum of the effect modifier. For example, if the mortality associated with NMSC is modified by the comorbidity level of the patients it is clinically important to distinguish patients according to comorbidity, and therefore adjustment for comorbidity level should not be done. Rather, the mortality of NMSC for each level of comorbidity should be reported.

The term effect modification is often confused with "interaction", a term used in statistics to refer to departure of the relation from the underlying statistical model (71). Accounting for statistical interaction is a tool to improve a statistical model and is not necessarily clinically meaningful.

Age, gender and comorbidity level potentially may have an effect on the relationship between NMSC and mortality. Therefore, we stratified our analyses on age (in groups: 18-60, 61-70, 71-80, 81+ years), gender, and level of comorbidity (CCI) (study Ia). Patients with first primary NMSC tumours from the Gerda Frentz cohort were considered exposed, with the exposure further subdivided into BCC and SCCs. The "unexposed" group was comprised of population controls identified from the Danish Civil Registration System. The outcome was mortality and the association was measured by the mortality rate ratio.

Statistical analyses

In studies I, Ia and II, we constructed mortality curves for NMSC patients according to the tumour type (studies I, Ia, II), location (study I), and histological subtype (study I); analogous curves for population controls were used for comparison. Cox's proportional hazards regression was used to compute the total mortality rate ratio (MRR) and associated with 95-percent confidence interval (CI), comparing NMSC patients with the population controls. The assumption of proportional hazards was assessed graphically and found appropriate for all Cox models (84).

In study II, we computed the cumulative one-, five- and ten- year mortality for selected subgroups of NMSC patients and the population controls using the Kaplan Meier life-table method (85). In addition, we compared the MRR computed for patients with first primary NMSC in the Gerda Frentz Cohort (GFC) with the MRR for patients with first primary NMSC in the Danish Cancer Registry (DCR), using a Mantel-Haenszel (M-H) estimate of their ratio, and controlling for age and gender (86). The underlying assumption of MRR homogeneity across categories of age and gender was fulfilled.

In study III, we used conditional logistic regression to compute odds ratios (OR) for NMSC according to the chronic diseases overall and for each category of chronic disease. Because, we used risk-set sampling to select matched controls, the estimated exposure ORs can be interpreted as estimates of the incidence rate ratios (IRR) (71). To evaluate the presence of surveillance bias, we compared the risk of NMSC across levels of the Charlson Comorbidity Index and compared risk of high-risk versus low-risk tumours (87). To examine potential selection bias, we conducted the analyses stratified by age groups.

In study IV, we computed the standardized mortality ratio (SMR), defined as the ratio of the observed to the expected number of deaths, and based on the assumption that the observed number of deaths followed a Poisson distribution. To obtain the expected number of deaths, gender-specific death rates, computed according to 5-year age groups and 5-year calendar periods, were multiplied by the corresponding person-years of the NMSC patients. We examined the total- and cause-specific mortality, stratified by gender, time since diagnosis and according to a prior history of cancer other than NMSC.

Statistical analyses were performed using STATA® (version 9.0, STATA, College Station, Texas, USA) and SAS® software (version 8.2; SAS Institute Inc., Cary, NC, USA).

Results

Study I:

We identified 3209 patients with NMSC: 2120 (66%) had noduloulcerative BCC, 791 (25%) superficial BCC, 97 (3%) morpheaform BCC, 74 (3%) Bowen's disease, 116 (3%) SCC and 11 had multiple (>5) carcinomas.

Total mortality

Table III summarizes the total mortality among patients with BCC stratified according to histological subtype, SCC and multiple carcinomas compared with the population controls.

Table III: Histological type and total mortality of NMSC patients and population controls.

Histological diagnosis of carcinoma	N	Mortality rate per 100 person-years [95% CI]	Crude Mortality Rate Ratio (MRR) [95% CI][1]	Adjusted Mortality Rate Ratio (MRR) [95% CI][2]
Nodular and ulcerative BCC				
Controls	20909	5.4 [5.3-5.6]	1.0 (ref)	1.0 (ref)
Patients	2120	5.1 [4.8-5.5]	0.93 [0.87-1.00]	0.88 [0.81-0.94]
Superficial BCC				
Controls	7870	3.8 [3.7-4.0]	1.0 (ref)	1.0 (ref)
Patients	791	2.7 [2.3-3.1]	0.71 [0.61-0.83]	0.69 [0.60-0.81]
Morpheaform BCC				
Controls	964	5.1 [4.6-5.6]	1.0 (ref)	1.0 (ref)
Patients	97	4.7 [3.4-6.6]	0.94 [0.67-1.33]	1.01[0.71-1.42]
Bowen disease				
Controls	740	6.6 [5.9-7.3]	1.0 (ref)	1.0 (ref)
Patients	74	5.5 [3.9-7.9]	0.84 [0.58-1.21]	0.70 [0.48-1.01]
SCC				
Controls	1136	9.2 [8.5-9.9]	1.0 (ref)	1.0 (ref)
Patients	116	14.8 [12-18]	1.63 [1.30-2.04]	1.32 [1.05-1.65]
Multiple Carcinoma				
Controls	110	1.6 [0.9-2.6]	1.0 (ref)	1.0 (ref)
Patients	11	2.2 [0.5-8.8]	1.40 [0.32-6.14]	0.53 [0.12-2.42]

[1] The Mortality Rate Ratio and associated 95 percent confidence interval were computed using Cox's regression.
[2] The Mortality Rate Ratio and associated 95 percent confidence interval were computed using Cox's regression. The Mortality Rate Ratio was adjusted for co-morbidity (CCI) and civil status (Records of civil status were missing for 20 percent).

In addition, we found a reduced mortality among patients with nodular and ulcerative BCC located on the trunk (adjusted MRR = 0.79 (95% CI, 0.63-0.99)) and among patients with superficial BCC located on extremities (adjusted MRR = 0.54 (95% CI, 0.35-0.83)). No substantial difference was found among SCC patients with different tumour locations.

Cause-specific mortality

Table IV summarizes the cause-specific mortality among patients with BCC and SCC compared with the population controls for the relevant categories.

Table IV: Cause-specific mortality among patients with NMSC and population controls

Causes of death (ICD-10)		**Basal cell carcinomas** 10 year follow up (1995-2004)			
		N	Mortality rate/100 person-years [95% CI]	MRR[1]	95% CI
Overall mortality	Controls	11087	4.97[4.87-5.06]	1.0 (ref)	
	Patients	1019	4.40[4.14-4.68]	0.89	0.83-0.95
Heart disease	Controls	2705	1.21[1.16-1.25]	1.0 (ref)	-
	Patients	243	1.04[1.00-1.18]	0.86	0.75-0.99
Vascular disease of the circulatory system	Controls	673	0.30[0.28-0.32]	1.0 (ref)	-
	Patients	45	0.19[0.14-0.26]	0.64	0.47-0.87
Gastrointestinal disease, other than cancer	Controls	476	0.21[0.19-0.23]	1.0 (ref)	-
	Patients	28	0.12[0.08-0.17]	0.57	0.37-0.83
Other malignant disease, except skin cancer	Controls	2464	1.10[1.06-1.14]	1.0 (ref)	-
	Patients	257	1.10[1.00-1.25]	1.01	0.88-1.14
Malignant melanoma	Controls	28	0.01[0.01-0.02]	1.0 (ref)	-
	Patients	8	0.03[0.02-0.07]	2.75	1.08-6.20
Causes of death (ICD-10)		**Squamous cell carcinomas** 10 year follow up (1995-2004)			
		N	Mortality rate/100 person-years [95% CI]	MRR[1]	95% CI
Overall mortality	Controls	661	9.21[8.54-9.94]	1.0 (ref)	
	Patients	86	14.9[12.0-18.4]	1.61	1.27-2.02
Heart disease	Controls	171	2.38[2.05-2.76]	1.0 (ref)	-
	Patients	23	3.97[2.64-5.97]	1.71	1.05-2.65
Bronchitis, emphysema, and asthma	Controls	31	0.43[0.30-0.61]	1.0 (ref)	-
	Patients	5	0.86[0.36-2.08]	2.00	0.61-5.19
Gastrointestinal disease, other than cancer	Controls	32	0.44[0.31-0.63]	1.0 (ref)	-
	Patients	4	0.69[0.26-1.84]	1.55	0.40-4.38
Other malignant disease, except skin cancer	Controls	84	1.17[0.94-1.45]	1.0 (ref)	-
	Patients	11	1.90[1.05-3.43]	1.63	0.78-3.06

[1] The Mortality Rate Ratio and associated 95 percent confidence interval were computed by direct calculation of the Incidence Rate Ratio.

Study Ia:

We identified 4187 first primary NMSC cases, of which 3801 (91%) were BCC and 386 (9%) were SCC.

Analyses among patients with first primary BCC tumours, stratified by age, gender and comorbidity

The 1- and 10- year cumulative mortality increased with increasing age and comorbidity level; mortality was higher among males than among females. The 10-year mortality rate ratio was modestly higher among younger compared with older patients (1.06; 95% CI: 0.86-1.30 among 18-60-year-olds versus 0.85; 95% CI: 0.78-0.93 among 71-80-year-olds). The 10-year MRR was also higher among males (0.97; 95% CI: 0.90-1.05) compared with females (0.82; 95% CI: 0.76-0.89), and it did not change substantially according to Charlson score (0.88; 95% CI: 0.83-0.94, for CCI=0, 0.99; 95% CI: 0.87-1.14, for CCI of 1 and 2, and 0.88; 95% CI: 0.69-1.11, for CCI>2) (table V).

Analyses among patients with first primary SCC tumours, stratified by age, gender and comorbidity

The 1- and 10- year cumulative mortality increased with increasing age and comorbidity level and was modestly higher among males than among females. The 1-year mortality rate ratio was higher among younger compared with the older patients (6.67; 95% CI: 0.42-52 among 18-60-year-olds versus 1.30; 95% CI: 0.89-1.89 for those older than 80 years); however the 10-year MRR was lower among the patients in the youngest age-groups compared with those in older ones. The effect on mortality was lower among males compared with females (10-year MRR: 1.21; 95% CI: 1.03-1.43 versus 10-year MRR: 1.31; 95% CI: 1.07-1.60). The MRR did not change substantially according to Charlson score, with 10-year MRRs 1.27; 95% CI: 1.10-1.47, 1.19; 95% CI: 0.88-1.61, 1.18; 95% CI: 0.74-1.89 for the CCI categories marking increasing comorbidity (table VI).

Table V: Mortality and mortality rate ratios (MRR) among incident basal cell carcinoma (BCC) patients and their age-, gender- and residence matched population controls according to age, gender and level of comorbidity, as measured on the diagnosis/index date

		Age groups			
		18-60	61-70	71-80	81+
Number of BCC patients		1279 (34%)	894 (24%)	1028 (27%)	600 (16%)
Number of population controls		12727 (34%)	8886 (24%)	10277 (27%)	5753 (16%)
1 year	Cumulative mortality patients, % (95% CI)[1]	0.6 (0.3-1.3)	2.0 (1.3-3.2)	4 (3.0-5.5)	11 (8.8-14)
	MRR[2]	0.83 (0.38-1.79)	0.82 (0.51-1.33)	0.71 (0.52-0.98)	0.79 (0.61-1.01)
	MRR adjusted[3]	0.82 (0.38-1.78)	0.81 (0.50-1.31)	0.70 (0.51-0.95)	0.78 (0.61-1.01)
10 year	Cumulative mortality patients, % (95% CI)	9 (7.6-10.7)	26 (23-29)	50 (47-53)	83 (80-86)
	MRR	1.06 (0.86-1.30)	0.89 (0.78-1.02)	0.85 (0.78-0.93)	0.94 (0.85-1.03)
	MRR adjusted	1.06 (0.86-1.30)	0.90 (0.78-1.03)	0.85 (0.78-0.93)	0.93 (0.85-1.02)

		Gender	
		Male	Female
Number of BCC patients		1813 (48%)	1988 (52%)
Number of population controls		17887 (48%)	19756 (52%)
1 year	Cumulative mortality patients, % (95% CI)	3.8 (3.0-4.8)	3.3 (2.6-4.2)
	MRR	0.78 (0.61-1.00)	0.78 (0.61-1.01)
	MRR adjusted	0.74 (0.58-0.95)	0.78 (0.60-1.00)
10 year	Cumulative mortality patients, % (95% CI)	41 (39-44)	31 (29-33)
	MRR	1.00 (0.92-1.08)	0.86 (0.79-0.94)
	MRR adjusted	0.97 (0.90-1.05)	0.82 (0.76-0.89)

		Charlson score		
		0	1-2	>2
Number of BCC patients		3304 (87%)	403 (11%)	94 (2%)
Number of population controls		32864 (87%)	3957 (11%)	822 (2%)
1 year	Cumulative mortality patients, % (95% CI)	3 (2-3)	7 (5-10)	16 (10-25)
	MRR	0.77 (0.62-0.95)	0.81 (0.55-1.18)	0.72 (0.43-1.23)
	MRR adjusted	0.76 (0.61-0.94)	0.78 (0.53-1.14)	0.74 (0.43-1.25)
10 year	Cumulative mortality patients, % (95% CI)	31 (30-33)	60 (56-65)	81 (72-88)
	MRR	0.91 (0.85-0.97)	1.01 (0.89-1.16)	0.90 (0.71-1.14)
	MRR adjusted	0.88 (0.83-0.94)	0.99 (0.87-1.14)	0.88 (0.69-1.11)

[1] The cumulative mortality and associated 95% CI for patients with BCC was computed by the Kaplan-Meier life-table method.
[2] Cox's regression analysis was used to compute the hazard ratio as a measure of the mortality rate ratio (MRR) and associated 95% CI of patients compared with population controls.
[3] Cox's regression analysis was used to compute the hazard ratio as a measure of the mortality rate ratio (MRR) and associated 95% CI of patients compared with population controls, adjusted for age, gender and level of comorbidity, respectively.

Table VI: Mortality and mortality rate ratios (MRR) among patients with incident squamous cell carcinoma (SCC) patients and their age-, gender- and residence matched population controls, according to age, gender and level of comorbidity, as measured on the diagnosis/index date

		Age groups			
		18-60	61-70	71-80	81+
Number of SCC patients		30 (8%)	57 (15%)	133 (34%)	166 (43%)
Number of population controls		300 (8%)	570 (16%)	1314 (36%)	1487 (41%)
1 year	Cumulative mortality patients, % (95% CI)[1]	3.3 (0.5-21)	3.5 (0.1-13)	5.3 (2.5-11)	19 (14-26)
	MRR[2]	4.98 (0.45-55)	1.43 (0.32-6.27)	0.79 (0.37-1.72)	1.34 (0.92-1.94)
	MRR adjusted[3]	6.67 (0.42-52)	1.29 (0.29-5.75)	0.70 (0.32-1.52)	1.30 (0.89-1.89)
10 year	Cumulative mortality patients, % (95% CI)	10 (3.3-28)	37 (26-51)	68 (60-76)	92 (87-96)
	MRR	0.88 (0.27-2.87)	1.14 (0.72-1.78)	1.38 (1.11-1.72)	1.28 (1.09-1.52)
	MRR adjusted	0.90 (0.28-2.95)	1.08 (0.68-1.69)	1.30 (1.04-1.62)	1.26 (1.06-1.49)

		Gender	
		Male	Female
Number of SCC patients		243 (63%)	143 (37%)
Number of population controls		2297 (63%)	1374 (37%)
1 year	Cumulative mortality patients, % (95% CI)	11 (7.4-15)	11 (7.0-18)
	MRR	1.22 (0.81-1.84)	1.30 (0.77-2.18)
	MRR adjusted	1.12 (0.75-1.69)	1.22 (0.72-2.06)
10 year	Cumulative mortality patients, % (95% CI)	67 (61-73)	73 (66-80)
	MRR	1.24 (1.06-1.46)	1.29 (1.05-1.58)
	MRR adjusted	1.21 (1.03-1.43)	1.31 (1.07-1.60)

		Charlson score		
		0	1-2	>2
Number of SCC patients		298 (77%)	62 (16%)	26 (7%)
Number of population controls		3067 (84%)	500 (14%)	104 (3%)
1 year	Cumulative mortality patients, % (95% CI)	9 (6-13)	16 (9-28)	23 (11-44)
	MRR	1.19 (0.79-1.78)	1.13 (0.58-2.19)	1.03 (0.42-2.52)
	MRR adjusted	1.14 (0.76-1.72)	1.25 (0.64-2.43)	1.05 (0.43-2.60)
10 year	Cumulative mortality patients, % (95% CI)	66 (60-71)	79 (68-88)	88 (73-97)
	MRR	1.23 (1.06-1.43)	1.13 (0.84-1.52)	1.14 (0.72-1.80)
	MRR adjusted	1.27 (1.10-1.47)	1.19 (0.88-1.61)	1.18 (0.74-1.89)

[1] The cumulative mortality and associated 95% CI for patients with BCC was computed by the Kaplan-Meier life-table method.

[2] Cox's regression analysis was used to compute the hazard ratio as a measure of the mortality rate ratio (MRR) and associated 95% CI of patients compared with population controls.

[3] Cox's regression analysis was used to compute the hazard ratio as a measure of the mortality rate ratio (MRR) and associated 95% CI of patients compared with population controls, adjusted for age, gender and level of comorbidity, respectively.

Study II:

We identified 9709 patients with NMSC registered in the Gerda Frentz Cohort (GFC) in 1995; these were comprised of a mixture of first primaries (n=1898), subsequent new cases (n=2405) and cases with an unknown history of NMSC (n=5406). In the same year (1995), 4925 first primary cases of NMSC were registered in the Danish Cancer Registry (DCR). After linking the GFC with the DCR, we found that 1121 (10%) patients were registered only in the DCR; 3804 (35%) patients were registered in both the GFC and the DCR, and 5905 (55%) patients were registered only in the GFC.

Mortality among patients registered in the GFC

We found no substantial difference in one-, five- and ten-year cumulative mortality, from 1996 through 2006 among patients with first primary BCC and SCC, new subsequent BCC and SCC and BCC and SCC patients with an unknown history of NMSC.

Mortality among patients with first primary BCC and SCC in the GFC and the DCR

Between 1996 and 2006, we found no major difference in one-, five-, or ten-year cumulative mortality among patients with first primary BCC and SCC, as inferred from the information in the GFC and in the DCR. Compared with the respective matched population controls, the MRR among patients with first primary BCC was 0.91 (95% CI: 0.84-0.98) in the GFC and 0.96 (95% CI: 0.91-1.00) in the DCR (M-H p-value=0.85). The MRR among patients with first primary SCC was 1.29 (95% CI: 1.05-1.56) in the GFC and 1.36 (95% CI: 1.22-1.52) in the DCR (M-H p-value=0.10).

Study III:

We identified 4187 first primary NMSC cases, comprised of BCC (N= 3801, 91%) and SCC (N= 386, 9%).

Chronic diseases as risk factors for NMSC

The prevalence of previous hospitalization for chronic diseases among patients with NMSC and population controls, and the associated incidence rate ratios for BCC and SCC are shown in table VII.

Chronic diseases and the overall risk of NMSC

Eighty-seven percent of all patients with BCC had no record of a chronic disease before the date of diagnosis in 1995; the remaining 13% had at least one chronic condition that required hospitalization. A similar distribution of chronic diseases was observed among the population controls, with an overall IRR for BCC of 1.03 (95% CI: 0.93-1.14) for any chronic disease versus none (table VII, bottom). Compared with comorbidity-free patients (CCI=0), the IRR were 1.01 (95% CI: 0.90-1.13) among patients with the medium comorbidity level (CCI = 1-2) and 1.14 (95% CI: 0.92-1.42) among patients with high comorbidity level (CCI>2) (data not shown). After excluding disease categories which are known to increase the risk for NMSC, the IRR for BCC was 0.97 (95% CI: 0.90-1.05) for any chronic disease versus none (table VII, bottom).

Among the patients with SCC, 77% had no hospitalizations for chronic diseases before the date of diagnosis in 1995 and 23% had at least one chronic disease requiring hospitalization. The corresponding proportions among the population controls were 83% and 17%, with an overall IRR for SCC of 1.47 (95% CI: 1.14-1.91) for any chronic disease versus none (table VII, bottom). Compared with comorbidity-free patients (CCI=0), the IRR was 1.27 (95% CI: 0.95-1.71) among SCC patients with medium comorbidity level (CCI=1-2) and 2.46 (95% CI: 1.55-3.90) among those with high comorbidity level (CCI>2) (data not shown). After excluding disease categories which are known to increase the risk for NMSC, the IRR for SCC was 1.11 (95% CI: 0.86-1.43) for any chronic disease versus none (table VII, bottom).

High-risk versus low-risk BCC and SCC[2]

Similar proportions of cases and controls had a history of hospitalization with a chronic disease when defining risk profile for BCC and SCC according to tumour size ($\geq$ 20mm versus < 20mm). When defining BCC aggressiveness by its histological profile, the IRR for morpheaform BCC was modestly lower (IRR of 0.88 (95% CI: 0.68-1.14) than for noduloulcerative and superficial BCC (IRR of 1.06 (95% CI: 0.95-1.18), when comparing patients having any chronic disease with patients having none. When defining SCC aggressiveness according to its degree of differentiation, the IRR was 1.64 (95% CI: 1.18-2.28) for a high-risk SCC and 1.37 (95% CI: 0.86-2.18) for a low-risk SCC, when comparing patients having any chronic disease with patients having none.

The impact of chronic diseases on the overall risk of NMSC according to age

Chronic diseases were recorded in similar proportions among BCC cases and controls in all age groups. The IRRs for BCC was 1.03 (95% CI: 0.81-1.32) in those below 61 years of age, 1.01 (95% CI: 0.89-1.15) in those between 61-80 years of age and 1.09 (95% CI: 0.89-1.33) in those aged 81 years or older, comparing patients with any chronic disease versus none. Chronic diseases were recorded in similar proportions among SCC cases and controls who were younger than 61 years of age, with an IRR for SCC of 0.82 (95% CI: 0.18-3.66). SCC patients older than 61 years had a higher prevalence of at least one chronic disease requiring hospitalization compared with the controls, with an IRR for SCC of 1.88 (95% CI: 1.33-2.66) in those between 61-80 years of age and an IRR for SCC of 1.18 (95% CI: 0.79-1.76) in those aged 81 years or older, when comparing patients having any chronic disease with patients having none.

[2] We classified tumours into high-risk and low-risk groups according to tumour size for both BCC and SCC (low-risk as below 20 mm and high-risk as above 20 mm), histological features of BCC (nodular, superficial and ulcerative were considered low risk whereas morpheaform BCC were considered high risk) and level of differentiation of SCC (well differentiated tumours were considered low-risk and poor to moderately differentiated ones were considered high-risk).

Table VII: Distribution of chronic diseases in cases with first primary Non-melanoma skin cancer and population controls

	Basal Cell Carcinomas			Squamous Cell Carcinomas		
	Number of cases (N= 3801)	**Number of controls (N= 37643)**	**Incidence Rate Ratio (IRR) (95% CI)**	**Number of cases (N= 386)**	**Number of controls (N= 3671)**	**Incidence Rate Ratio (IRR) (95% CI)**
Hospital diagnoses before index date: Cardiovascular disease (CVD)	239 (6%)	2267 (6%)	1.05 (0.91-1.20)	44 (11%)	338 (9%)	1.23 (0.87-1.73)
Chronic pulmonary disease	76 (2%)	759 (2%)	1.00 (0.78-1.26)	17 (4%)	94 (3%)	1.70 (0.99-2.91)
Connective tissue disease	49 (1.3%)	362 (1.0%)	1.34 (0.99-1.82)	6 (2%)	35 (1%)	1.41 (0.55-3.61)
Moderate to severe renal disease	14 (0.4%)	104 (0.3%)	1.34 (0.76-2.33)	2 (0.5%)	8 (0.2%)	2.5 (0.53-12)
Organ transplants	4 (0.1%)	5 (0.01%)	8.00 (2.15-30)	1 (0.3%)	1 (0.03%)	10 (0.63-160)
Any solid cancer except skin cancer	129 (3%)	1149 (3%)	1.12 (0.93-1.35)	20 (5%)	124 (3%)	1.53 (0.94-2.49)
Leukaemia	4 (0.1%)	32 (0.1%)	1.25 (0.44-3.53)	5 (1%)	7 (0.2%)	7.75 (2.35-26)
Lymphoma	11 (0.3%)	44 (0.1%)	2.50 (1.29-4.84)	3 (0.8%)	7 (0.2%)	3.86 (0.99-15)
Any severe skin disease	18 (0.5%)	141 (0.4%)	1.20 (0.73-1.99)	6 (2%)	11 (0.3%)	5.28 (1.95-14)
The overall association between chronic diseases and NMSC: Any chronic disease	506 (13%)	4861 (13%)	1.03 (0.93-1.14)	89 (23%)	610 (17%)	1.47 (1.14-1.91)
Any chronic disease excluding disease categories which are known to elevate the risk of NMSC[1]	452 (12%)	4095 (11%)	0.97 (0.90-1.05)	82 (21%)	534 (15%)	1.11 (0.86-1.43)

[1] Excluding connective tissue disease, moderate to severe renal disease, organ transplants, solid cancers, leukaemia, lymphoma, and severe skin disease.

Study IV:

In the period from 1978 to 2001, we identified 82,837 BCC patients and 13,453 SCC patients in the Danish Cancer Registry. The 1486 (1.8%) of the BCC patients who developed a subsequent SCC, and the 972 (7.2%) of the SCC patients who subsequently developed a BCC, were classified as mixed NMSC.

Mortality among patients with primary NMSC

Among BCC patients, the overall mortality rate was 4.9 (95% CI: 4.8-4.9) per 100 person-years, which was slightly lower than mortality in the general population (SMR, 0.97; 95% confidence interval (CI): 0.96-0.98); decreased SMRs were seen for deaths from cardiovascular diseases, chronic obstructive pulmonary disease (COPD), diseases of the digestive tract, and diabetes. Death rates due to suicide and cancer were increased. After restricting the analyses to patients without a prior history of cancer the overall mortality rate was further reduced to 4.6 (95% CI: 4.5-4.6) per 100 person-years. The corresponding SMR was 0.92 (95% CI: 0.91-0.94), and generally the cause-specific mortality from cancer causes were reduced. However, we still found an increased mortality among the BCC patients for deaths caused by cancer of the larynx, trachea and bronchus with a mortality rate of 0.3 (95% CI: 0.2-0.3) per 100 person-years and a SMR of 1.10; 95% CI: 1.04-1.16. Furthermore, we found an increased mortality from cancer of the skin with a mortality rate of 0.03 (95% CI: 0.03-0.04) per 100 person-years and a SMR of 2.05; 95% CI: 1.75-2.38.

Among the SCC patients, the overall mortality rate was 9.8 (95% CI: 9.6-10) per 100 person-years.The overall mortality was greater than mortality in the general population (SMR, 1.30; 95% CI: 1.26-1.33), with elevated SMRs for deaths from cardiovascular diseases, COPD, genital diseases, acute infections, pneumonia and cancer. Elevated SMRs for deaths from acute infections, pneumonia and genital diseases was observed mainly among male SCC patients. After restricting the analyses to patients without a prior history of cancer, the overall mortality rate was further reduced to 9.2 (95% CI: 9.0-9.5) per 100 person-years. The corresponding SMR was 1.23 (95% CI: 1.20-1.26). Elevated SMRs were still seen for deaths from the following cancers: Cancer of the rectum and anal region (mortality rate of 0.5 (95% CI: 0.4-0.6) per 100 person-years with a corresponding SMR of 6.44 (95% CI: 5.76-7.18)); cancer of the larynx, trachea and bronchus (mortality rate of 0.5 (95% CI: 0.4-0.5) per 100 person-years with a corresponding SMR of 1.50 (95% CI: 1.34-1.68)); cancer of the buccal cavity (mortality rate of 0.1 (95% CI: 0.09-0.1) per 100

person-years with a corresponding SMR of 2.30, (95% CI: 1.81-2.89)); cancer of the skin (mortality rate of 0.5 (95% CI: 0.4-0.5) per 100 person-years with a corresponding SMR of 22.9 (95% CI: 20.3-25.6)) and leukaemia (mortality rate of 0.2 (95% CI: 0.1-0.2) per 100 person-years with a corresponding SMR of 1.52 (95% CI: 1.25-1.83)).

The overall and cause specific mortality pattern of mixed NMSC was similar to that of SCC patients.

Variation with time since diagnosis

The overall SMR among female BCC patients increased with increasing time since diagnoses. The SMR was 0.81 (95% CI: 0.77-0.86) within the first year of follow up, 0.93 (95% CI: 0.91-0.96) within 1-4 years, 0.99 (95% CI: 0.96-1.02) within 5-9 years and 1.02 (95% CI: 0.99-1.06) after 10 or more years since diagnosis. A similar trend was found among male BCC patients, and the opposite trend was found among SCC patients of either gender.

Strengths and weaknesses of the studies

Before concluding that results of our studies stem from underlying causal associations, we need to critically evaluate how selection bias, information bias, confounding, and random variation could affect our findings (30) (figure 4). Studies I, Ia, II and IV are cohort studies and study III is a case-control study.

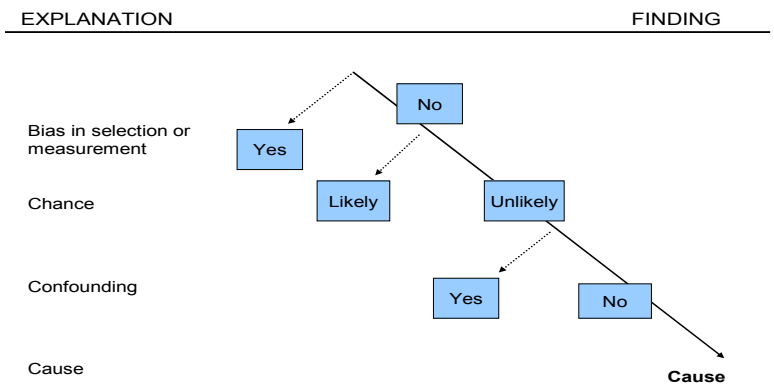

Figure 4. Association and cause from Fletcher "Clinical Epidemiology *The Essentials*" (30).

Selection bias

Generally, the high degree of incomplete registration of NMSC could give rise to selection in our study population. Since we used different source populations and study designs in our studies we will discuss selection bias and how we have considered the problem for each study separately. In cohort studies (I, Ia, II, IV), selection bias could also arise due to loss to follow-up. However, loss to follow-up is neglible because each person's status can be verified through the high quality Civil Registration System (82).

The population of **study I** consisted of NMSC patients seen at private or public outpatient dermatology clinics who were registered in the Gerda Frentz Cohort (GFC). The degree of selection bias in this cohort would depend of differences in mortality between patients referred to office settings and patients referred to hospitals for the NMSC treatment. We speculated that patients treated in office settings were healthier and therefore more likely to survive than the overall population of NMSC patients as registered in the Danish Cancer Registry. This would cause the

mortality to be underestimated; and this hypothesis was supported by the observation of a reduced cause-specific (cardiovascular and gastrointestinal) mortality among BCC patients.

Therefore, in **study II**, we compared mortality among patients with first primaries registered in the GFC with mortality among patients with first primaries registered in the DCR. Contrary to our expectation, we found similar mortality among patients registered in the two databases, arguing against the presence of this selection bias in study I. However, the incomplete registration of NMSC in the DCR (78, 88) makes it a questionable gold standard, and if this incomplete registration is differential with regard to prognosis of NMSC patients, selections bias cannot be ruled out.

The population of NMSC cases in **study III** consisted of first primaries registered in the GFC. Selection in this case series (which is the Gerda Frentz cohort in the cohort studies) could arise if the association between hospitalization for a chronic disease and risk of NMSC differed between registered and not-registered cases. Since BCC in particular is rarely fatal, in severely diseased patients clinicians potentially could deem these cancers trivial and therefore pay less medical attention to them. This potential under-ascertainment of BCC cases with severe diseases in our case series would lead to underestimation of the overall effect of hospitalization for chronic diseases on the risk of BCC (89). As an indicator for selecting out the severely diseased BCC patients, we used age because we would expect a higher degree of selection among older severely diseased patients compared with the younger ones, and therefore a lower risk for BCC among older patients hospitalized for chronic diseases. However, in our study, risk of BCC was similar in younger and older age groups. Provided age was an appropriate indicator, our results do not provide evidence for a severe selection bias.

This selection could also cause bias in the cohort designs (**study I, Ia, II and IV**). If patients registered with a NMSC are healthier and therefore survive longer than the non-registered NMSC patients, the association between exposure (NMSC) and outcome (mortality) could differ between participants and non-participants of the study. Supportive for this hypothesis was the reduced mortality among BCC patients compared with the general population, which was found in all studies. We examined this potential selection in **study IV** by stratifying NMSC patients into two groups; those who had had another primary cancer before their NMSC and those who had not. Mortality was only slightly different in the two groups of BCC patients, suggesting the presence of a selection bias. If

all BCC cases occurring among patients with severe cancers were recorded we would expect a greater difference in mortality and a larger increase in mortality compared with the general population, as we found among SCC patients.

Information bias

If information collected about study subjects is erroneous, information bias arise (71). This can result in misclassification of the exposure, the outcome, or the confounding factors. Systematic errors arise if this misclassification is differentially distributed among comparison groups, and it can either under- or overestimate the effects (72). Again, because of the high degree of incomplete registration of NMSC, information bias could easily be present in our studies.

In **study I**, **Ia and IV** information bias could stem from erroneous classification of first primary NMSC cases and subsequent cases. A high degree of incomplete registration makes the history of NMSC either unknown or untrustworthy, making it impossible to distinguish between first primaries and new subsequent cases. Mixing of first primaries and new subsequent cases may cause bias in a mortality study because patients with new subsequent disease are better survivors (30). This bias would underestimate the mortality of NMSC. The observation of reduced mortality among BCC patients speaks for the presence of this type of bias.

Therefore, in **study II**, we examined any differences in mortality between first primaries and new subsequent cases of NMSC registered in the GFC. Contrary to our expectation, the two groups had similar relative mortality, which is evidence against the speculation that reduced mortality was an artefact of the information bias.

In **study III**, information bias may have occurred as a result of differential misclassification, i.e., if either the exposure (chronic diseases) is misclassified differentially according to a person's disease status or the disease (NMSC) is misclassified differentially according to a person's exposure status (71, 90). For example, diseased patients could be more likely to have a NMSC detected than healthy people (e.g., surveillance bias (90)). This could explain the observed association between hospitalization for chronic diseases and the risk of SCC. However, if important, this bias would have to be differential between BCC and SCC patients, and we did not find an association between hospitalization for chronic diseases and risk of BCC. We evaluated the impact of surveillance bias in study III. We compared the risk of a high-risk (aggressive tumour behaviour) versus a low-risk

tumour among the hospitalized patients. If surveillance bias were present, we would expect a higher risk of a high-risk tumour than a low-risk tumour among those hospitalized with a chronic disease. However, the associations did not differ according to tumour size, histological subtype or level of differentiation of the NMSC, arguing against the surveillance bias.

Finally, in **studies I and IV**, with cause-specific mortality as the outcome, information bias may have occurred due to errors in coding of causes of death (91, 92). However, except for errors relating to the cause of death: "cancer of the skin", we would expect the errors in all other diagnoses to affect equally the NMSC patients and the general population (non-differential misclassification); such misclassification tends to produce underestimates of the true relative effects.

Confounding

In studies I-IV we controlled for the effects of age, gender and area of residence by matching, and in **study I** we adjusted the analyses for comorbidity and civil status (as a proxy for socio-economic position). However, our effect estimates could still be affected by residual, unmeasured, or unknown confounding in all four studies.

Residual confounding results from imperfect categorization and misclassification of one or more confounding variables, such as comorbidity. In order to control confounding by co-morbidity, we used the Charlson Comorbidity index, which was developed to predict 1-year patient mortality using co-morbidity data obtained from hospital chart review (83). The index includes 19 major chronic disease categories, and has now been widely adapted for use with hospital discharge data in ICD-based databases. The index has a high specificity but a more variable sensitivity, and is inferior to clinical data in measuring comorbidity (93). However, in terms of predicting life expectancy among NMSC patients, it has been found to be a valid prognostic instrument (77). The assumed selection bias among the BCC patients could result in different coding accuracy in the hospital discharge registry causing misclassification of the Charlson Comorbidity Index. If comorbidity is coded more accurately in the more diseased patients, this would lead to less accurate coding among BCC patients compared with the general population. Likewise, the assumed surveillance bias among SCC patients potentially could result in more accurate coding. This misclassification of comorbidity could lead to residual confounding in study I. Nevertheless, when controlling for

measured comorbidity we did not observe any major change in estimates among BCC patients in study I, which is an argument against residual confounding. At the same time, adjustment for comorbidity did produce a change in estimates among SCC patients, raising the possibility of residual confounding.

Residual confounding by socio-economic position is likely. We used civil status as a proxy for socio-economic position in **study I**. However, socio-economic position is also determined by income, education and occupation (94, 95) and therefore, we would expect some degree of misclassification of socio-economic position by civil status. We would expect this misclassification to be non-differential; however unmeasured differences between NMSC patients and the general population may have influenced our results.

Residual confounding due to mutually independent misclassification of two confounding categories (i.e., comorbidity and socio-economic position) will reduce the degree to which confounding can be controlled, and thus can cause either over- or underestimation of the true effect, depending on the direction of confounding (96).

Potential confounding by life style variables, such as UV-light exposure, smoking, physical activity and other variables measuring general health status, cannot be ruled out, since data on these variables were not available in any of the used data sources. Therefore, we were unable to adjust for differences in these variables across exposure categories, which may have influenced our results in **studies I, II and IV**.

A major limitation of **study III**, was the inability to account for the medication taken for the chronic diseases associated with an increased risk of NMSC. The individual chronic diseases that appeared to be associated with NMSC risk were those treated with immunosuppressive medications (e.g., prednisone, cyclosporine, azathioprine). Since immunosuppressive medications are also known to increase risk of NMSC (97, 98), this unmeasured confounding factor could partially explain the observed associations.

In **study Ia**, we examined whether the relationship between NMSC and mortality was different depending on the level of comorbidity. If comorbidity - the effect modifying variable - was subject

to misclassification, false positive or false negative estimates of effect modification may have appeared (99).

Random variation (chance)

Random variation, or chance, affects the precision of a study's effect estimates. We have used 95% confidence interval to reflect precision of our effect estimates.

Main conclusions

Based on the results in the four studies and an evaluation of potential biases, the following conclusions were drawn from the studies.

Study I

Total mortality and mortality from cardiovascular and gastrointestinal diseases are lower among BCC patients compared with the general population, an observation that may be explained by a healthier life style among BCC patients. Total mortality and mortality from cardiovascular diseases and cancer are higher among SCC patients compared with the general population. This suggests a different clinical course of BCC and SCC, and further supports the appropriateness of separating BCC and SCC into distinct disease entities. In addition, patients with superficial BCC seem to have a lower total relative mortality compared with patients who have other histological subtypes of BCC. Nevertheless, selection and information bias could also explain the findings.

Study Ia

Age modifies the association between SCC and mortality, and we found a 6-fold increased risk of dying among SCC patients younger than 60 years. Comorbidity as measured by the Charlson Comorbidity Index is not a major effect modifier of the NMSC-related mortality, although information bias from misclassification of comorbidity level cannot be completely ruled out.

Study II

Patients with first primary and new subsequent cases of NMSC registered in the Gerda Frentz Cohort (GFC) have similar ten-year mortality. Patients with first primary NMSC registered in the GFC have similar mortality as patients with first primary NMSC registered in the Danish Cancer Registry (DCR). Thus, differences in mortality between first primaries and new subsequent cases or different mortality among patients registered in different data repositories are not likely to explain an earlier finding of a reduced mortality among BCC patients. However, selection bias in the DCR may still have influenced our findings.

Study III

To our knowledge, this is the first study examining the overall impact of chronic diseases on NMSC risk. We found an increased risk of SCC among patients with a prior history of a chronic disease, requiring hospitalization, but no substantial increased risk of BCC. The positive association for SCC persisted even after excluding disease categories that are known to elevate the risk of NMSC. However, a major limitation is the inability to adjust for medications taken for the chronic diseases associated with an increased risk of NMSC (i.e., immunosuppressive treatments for immunological diseases). Therefore, we cannot completely rule out that the association observed represent a treatment effect.

Study IV

Our findings indicate a reduced mortality among patients with BCC which is likely explained by a healthy life style associated with sun exposure. An increased mortality among patients with SCC is likely explained by an increased mortality related to causes associated with alcohol use, smoking and an impaired immune function. This suggests a different clinical course of BCC and SCC, and further supports the appropriateness of separating BCC and SCC into two disease entities. However, we think that the increased cause-specific mortality from other cancers than skin cancer among both BCC and SCC patients suggests a common underlying biological mechanism with an aberrant condition in the immune system, allowing NMSC to develop.

Discussion in relation to the existing literature

In the following section, our results will be discussed in relation to the aims of this thesis and the existing literature.

Ten-year mortality in a prospective cohort of non-melanoma skin cancer patients in 1995

Our results contradict those reported from Finland (75) and America (76), where no difference in relative mortality was found among BCC patients and NMSC patients compared with the general population. The Finnish study included all BCC and SCC cases registered in the Finnish Cancer Registry from 1974 to 1981 and followed them during 10 years; the analyses were stratified according to gender and type of NMSC. The investigators in the American study collected NMSC cases up to 1982, did not stratify by type of NMSC but adjusted for multiple risk factors of mortality such as age, gender, education, smoking and health-related factors (body-mass index, alcohol use and exercise level). Although we controlled the effects of comorbidity, information on UV-light exposure, smoking, obesity and other lifestyle factors were not available in the National Patient Registry and therefore remained unmeasured. The differences in time span, settings, covariates used for adjustment and stratification according to type of NMSC could explain the disagreement between the various studies. Similar to our results is the reduced cause-specific mortality from circulatory diseases found in the American study (76), suggesting a healthier lifestyle, including low smoking and obesity levels among BCC patients.

As mentioned above, we controlled for comorbidity using the Charlson Comorbidity Index. A. J. Charles *et al.* (77) found it to be a valid prognostic instrument for predicting life expectancy among NMSC patients (77). Unfortunately, they did not stratify the analyses according to type of NMSC; however, they found a better than expected survival among comorbidity-free NMSC patients, thus supporting the finding of a reduced mortality among BCC patients after controlling for comorbidity.

Because, selection bias due to incomplete registration of NMSC, information bias due to misclassification of first primary and subsequent cases, and unmeasured confounding by lifestyle related factors could not be ruled out, no main conclusions were drawn from this study.

Do incident and new subsequent cases of non-melanoma skin cancer registered in a Danish prospective cohort study have different ten-year mortality?

To the best of our knowledge, this is the first study comparing mortality of first primary and new subsequent cases of NMSC. We think, it is of common interest to answer this question, as it is well known that registration and reporting of this cancer are incomplete (43, 44, 48, 67-69). Therefore, it is impossible to completely exclude persons with a history of NMSC from the cancer registries, and consequently a mixture of first primary and new subsequent cases of NMSC are studied.

We found similar mortality among patients with first primary and new subsequent cases of NMSC, suggesting that any resulting bias from this misclassification is likely to be slight. Further, we found a similar mortality among NMSC cases registered in two different data repositories in 1995, indicating that the unexpected result of a reduced mortality among BCC patients in study I could not be explained by the different case mix resulting from selection bias between NMSC cases registered by dermatologist compared with NMSC cases registered by all specialities in the Danish Cancer Registry.

Chronic diseases requiring hospitalization and risk of non-melanoma skin cancers

We conducted the first study examining the overall impact of chronic diseases on the NMSC risk. We further evaluated single diseases as risk factors for BCC and SCC, and our findings were in accordance with prior findings regarding connective tissue diseases (39, 100, 101), severe dermatological diseases (38, 41, 48), cancer diseases (42), leukaemia and lymphoma (102-105) and organ transplants (49-51). Because our risk estimates generally was not as strong as effect estimates shown by previous studies, we speculate that the findings of the latter may have been influenced by surveillance bias.

L. Mellemkjær *et al.* (39), in a cohort study to examine risk of cancer among rheumatoid arthritis (RA) patients found a relative risk of 1.4 for SCC and 1.3 for BCC among them; adjustments were made for age, gender and calendar period. However, if RA patients were receiving more medical attention compared with the general population, this surveillance bias could explain the association. In another cohort study of RA patients, E. F. Chakravarty *et al.* (40) stratified analysis on treatment

type (i.e., prednisone and TNF inhibitor use) and examined their risk of cancers. Their results suggested that NMSC risk was related to medications used to treat RA rather than RA itself. However, RA patients receiving prednisone or TNF inhibitors, may have been kept under closer surveillance compared with RA patients not receiving these medications, creating a surveillance bias that could explain the results. C. F. Paul *et al.* (41) investigated the effect of duration of exposure to cyclosporine and to previously administered anti-psoriatic treatments on the incidence of skin malignancies. The authors showed a clear effect by duration of treatment, indicating that the treatment is an important factor in the causal relation between psoriasis and NMSC. However, since NMSCs are more likely to be detected and reported in patients followed by dermatologists, the true risk may have been overestimated. This detection bias is further suggested by M. E. Ming *et al.* (73) who in a case-control study, found no increased risk of NMSC among patients with atopic dermatitis (AD). The authors avoided differential surveillance by selecting their control group among dermatological patients.

Unlike other studies, we did evaluate the possibility that our results were influenced by both surveillance and selection bias which is a strength compared with previous studies. However, we cannot be sure that the indicators used for measuring these biases entirely capture them (i.e., high-risk versus low-risk tumours for surveillance bias, and age for selection bias). Therefore, a nationwide clinical database with complete and valid registration of all NMSC cases, and with better data quality of data on chronic diseases is needed in order to access the true relation between comorbidity and risk of NMSC.

Mortality in a nationwide cohort of non-melanoma skin cancer patients registered in the Danish Cancer Registry from 1978 to 2001

In this first large study of mortality among NMSC patients, we found a reduced overall mortality among BCC patients which was due to lower mortality from smoking- and obesity-related causes, such as cardiovascular diseases, chronic obstructive lung diseases and diabetes. Mortality among SCC patients was increased due to more deaths from smoking-related causes, such as cardiovascular diseases, chronic obstructive lung diseases and cancer. These findings are in agreement with our earlier study (106).

Further, our findings support the notion that the outcome of NMSC is related to a certain lifestyle, which is different for BCC and SCC patients. We evaluated the presence of a "healthy patient effect" (similar to the "healthy-worker effect" (71, 107)). As expected, BCC patients had a better-than-average health status, which may reflect healthy life style potentially associated with sun exposure. This was not the case for SCC patients, which is in accordance with the increased mortality from chronic diseases associated with an unhealthy lifestyle (alcohol and smoking) and an impaired immune function. In particular, an association was found between deaths from cancers widely known to be related to humane papilloma virus (HPV), such as anal cancer, larynz cancer, cancer of the buccal cavity, and SCC. This finding, together with findings from another study reporting an increased risk of HPV related cancers after a diagnosis of SCC (44), support the evidence of HPV as a common risk factor for SCC in the general population.

How these differences relate to a common predisposition of both BCC and SCC patients to sun exposure is still unknown. In addition, a differential selection of BCC patients for reporting to the Danish Cancer Registry may also explain the apparent association between BCC and a reduced mortality. There is a need for a nationwide clinical database with registration of all NMSC cases, which would avoid incomplete registration and selection bias, and provide better information on lifestyle factors, underlying chronic diseases and comorbidity level. This would allow us to better assess risk factors and prognosis of NMSC patients.

Perspectives

Our studies have shown that chronic diseases have an impact on risk and mortality of NMSC. However, several aspects of chronic diseases as risk and prognostic factor for BCC and SCC are still poorly understood and need further examination. BCC seems to be associated with a healthy lifestyle, most probably related to sun exposure. SCC seems to be related to chronic diseases associated with alcohol use, smoking and an impaired immune function, and both BCC and SCC seem to be associated with other cancers. However, we cannot completely rule out that the outcome of these cancers is also related to factors associated with NMSC (the disease factor), since we found a difference in relative mortality according to histological subtype of BCC. Also, we cannot completely rule out that the outcome of these cancers is related to factors associated with the treatment of NMSC (the treatment factor); this was not evaluated in our studies due to lack of clinical data.

We found that provided a careful evaluation of biases observational studies of NMSC with use of clinical databases or registry data can be properly conducted. Our studies have exposed weaknesses and biases of studying NMSC using registry data, such as the incomplete registration (entailing the potential of selection and information bias) as well as lack of clinical details. In the future we would like to establish a nationwide clinical database with registration of all NMSC cases, thereby avoiding biases of incomplete registration and providing better quality of variables measuring lifestyle factors among NMSC patients, histological type of NMSC, treatment for NMSC, underlying chronic diseases and comorbidity. Using a complete NMSC clinical database, we would like to assess the true impact of chronic diseases on BCC and SCC risk. In order to control for medications used to treat the chronic diseases, linkage should be made to the Danish Prescription Database, administrated by Statistics Denmark.

An establishment of a nationwide clinical database with registration of all NMSC cases with information of specific treatments for NMSC would further allow us to access any relation between the treatment factors and outcome of NMSC.

Based on the findings in this thesis, BCC patients have a relatively good prognosis compared with other cancer patients, which may be explained by their healthier life style. However, to allow NMSC to develop, an aberrant condition in the body's immune system may exist. Therefore, it would be interesting to compare the risk and prognosis of immunological diseases and venous tromboembolism among NMSC patients with that of the general population. Further, in study I we suggested that a sufficient level of vitamin D among NMSC patients (owing to sun exposure as the common relation between level of vitamin D and NMSC) could contribute to the good prognosis among BCC patients compared with the general population. Supportive of this hypothesis would be a lower risk and a better prognosis for osteoporotic fractures among NMSC patients compared with the general population. This would be an interesting research topic to evaluate in the future.

A more complex way to assess health outcome in a particular population is to evaluate the quality of life (dissatisfaction level) (30) after the disease onset. Given the favourable prognosis of NMSC patients coupled with the finding of an increased risk of death from suicide among BCC patients, an analysis of the general quality of life (QOL) among these patients would be of common interest. The easiest way to assess this would be through a validated self-administered questionnaire (a survey). The few studies which have evaluated the QOL among these patients mainly measured as change in quality of life before and after treatment for NMSC (108-110). In the process, a validated QOL instrument for patients with NMSC was developed (109).

Summary

The incidence of NMSC, including BCC and SCC, is rising worldwide, and it is the most common cancer among Caucasians. Risk of NMSC is strongly associated with age and because of improved life expectancy among the elderly, an increase of NMSC is further expected. NMSC are largely attributable to factors related to sun exposure and skin sensitivity to sun exposure. However, given the high prevalence of these cancers, ongoing efforts to understand the underlying aetiology and means of preventing them are needed. Furthermore, because the older people bear the disproportionate share of the chronic disease burden, it is of common interest to know how chronic diseases influences and associates with risk and prognosis of NMSC. Any link between chronic diseases and NMSC will provide further insight into the clinical course and foster our understanding of NMSC. These findings will have a significant public health interest.

This thesis includes four observational studies conducted based on nationwide data from a prospectively assembled cohort and from a cancer registry. Further we made a linkage to the Danish Hospital Discharge Registry, the Civil Registration System and the National Death Register. The aims of the thesis were 1) to compare the total and cause-specific mortality of NMSC patients with that of the general Danish population according to the histological diagnosis, anatomic distribution and the number of NMSC in the individual, 2) to examine whether differences in mortality between first primary and new subsequent cases or different mortality among patients registered in different data repositories could explain a finding of a reduced mortality among BCC patients, 3) to evaluate overall associations between NMSC and chronic diseases and to examine whether a history of hospitalization for selected chronic diseases was a risk factor for a subsequent diagnosis of NMSC, 4) to examine total and cause-specific mortality of all NMSC patients registered in the Danish Cancer Registry in a 23-year period, as compared with that of the general Danish population.

In study I, we found a reduced mortality due to cardiovascular and gastrointestinal diseases among BCC patients (overall mortality rate ratio (MRR) 0.89, 95% CI: 0.83-0.95) and an increased mortality of cardiovascular diseases and cancer among SCC patients (overall MRR 1.61, 95% CI: 1.27-2.02). Adjustments for comorbidity and civil status did not change the estimates substantially for the BCC patients but did influence the estimates for the SCC patients. However, we were unable to rule out selection and information bias as an explanation for our findings.

In study II, we found similar ten-year mortality of patients with first primary and new subsequent cases of NMSC registered in the Gerda Frentz Cohort (GFC). Further, patients with first primary NMSC registered in the GFC had a similar mortality compared with patients with first primary NMSC registered in the Danish Cancer Registry (DCR). Thus, differences in mortality between first primaries and new subsequent cases or different mortality among patients registered in different data repositories are not likely to explain our findings in study I. However, we were unable to rule out selection bias in the Danish Cancer Registry.

In study III, we found an increased risk of SCC among patients with a history of hospitalization for a chronic disease (incidence rate ratio (IRR) 1.47, 95% CI: 1.14-1.91). The increased risk persisted after excluding patients with diseases known to elevate the risk of NMSC. We found no increased risk of BCC among patients with a history of hospitalization for a chronic disease (IRR = 1.03, 95% CI: 0.93-1.14), although the risk was elevated among patients with certain disease categories. Additional analyses suggested that surveillance or selection bias were unlikely explanations for the findings.

In study IV, we were able to reproduce a reduced mortality among BCC patients from cardiovascular, chronic pulmonary diseases and diabetes; and the analyses further indicated that BCC patients in Denmark may have a better health status compared with the general population. Further, we reproduced an increased mortality among SCC patients from cardiovascular, chronic pulmonary diseases, genital diseases and acute infections. Thus, BCC and SCC seem to be very different disease entities as far as their risk and prognosis are concerned. However, both BCC and SCC patients had an increased cause-specific mortality from cancers what may indicate a common aberrant condition in the immune system allowing NMSC and other cancers to develop.

Our studies have shown that after carefully evaluating biases, observational studies of NMSC with use of clinical databases or registry data can be properly conducted. Thus, in the future we hope to conduct larger studies risk factors, with complete and detailed data, and to assess more complex health outcomes among this group of patients.

Dansk resume

Forekomsten af non-melanom hudkræft (NMSC), der i denne afhandling omfatter Morbus Bowen, basal celle carcinom (BCC) og spinocellulært carcinom (SCC), er stigende. NMSC er den mest almindelige af alle kræfttyper blandt den hvide befolkning og de væsentligste risikofaktorer for udvikling af NMSC er sol eksponering og hudtype. Af øvrige risikofaktorer kan nævnes visse kroniske sygdomme, såsom autoimmune sygdomme, organ transplantation og andre cancere. Både kroniske sygdomme og NMSC forekommer hyppigere blandt den ældre befolkning, og det er derfor væsentligt at få undersøgt sammenhængen mellem kroniske sygdomme og NMSC. Hvis der er en sammenhæng vil denne eventuelt kunne bidrage til en øget indsigt i biologien og en bedre forståelse af sygdomsforløbet af NMSC til almen gavn for samfundet.

Formålene med PhD studiet var 1) at sammenligne total og årsagsspecifik dødelighed blandt NMSC patienter sammenlignet med den generelle danske befolkning i forhold til underliggende histologisk diagnose, antal og anatomisk lokalisation af canceren, 2) at undersøge om forskelle i dødelighed i mellem incidente og prevalente tilfælde eller forskelle i dødelighed blandt patienter registreret i forskellige registre kan forklare en reduceret dødelig blandt patienter med BCC, 3) at undersøge om kroniske sygdomme generelt og specifikt disponerer til udviklingen af NMSC, og 4) at sammenligne total og årsagsspecifik dødelighed blandt NMSC patienter sammenlignet med den generelle danske befolkning ved anvendelse af data fra Det Danske Cancerregister gennem en periode på 23 år.

I første studie fandt vi en reduceret dødelighed af kardiovaskulær og gastrointestinal sygdom blandt patienter med BCC (mortalitets rate ratio (MRR) på 0.89, 95% CI: 0.83-0.95) og en 60% øget dødelighed af specielt kardiovaskulær sygdom og cancersygdomme blandt patienter med SCC. Vi kunne dog ikke udelukke selektions- og informations bias som forklaring på vores resultater. I studie II fandt vi, at incidente og prevalente tilfælde af NMSC havde samme dødelighed, og samme dødelighed blandt NMSC patienter registreret i to forskellige registre (Gerda Frentz kohorten og det danske cancerregister). Derfor kan disse fejlkilder ikke forklare den reducerede dødelig blandt patienter med BCC, som vi fandt i studie I. I studie III fandt vi en øget risiko for SCC blandt patienter med kroniske sygdomme generelt (incidens rate ratio (IRR) på 1.47, 95% CI: 1.14-1.91) og risikoen var stadig øget, efter vi udelukkede de kroniske sygdomme, som vides at øge risikoen

for NMSC. Vi fandt ingen øget risiko for BCC blandt patienter med kroniske sygdomme generelt (IRR på 1.03, 95% CI: 0.93-1.14), selvom risikoen for BCC var øget blandt patienter med visse sygdomme. Resultaterne fra supplerende analyser synes at kunne udelukke væsentlige bias som forklaring på vores fund. I sidste studie, fandt vi en reduceret dødelighed blandt patienter med BCC af kardiovaskulære sygdomme, kronisk lungesygdom og diabetes. Derudover viste analyserne, at patienter med BCC tilsyneladende har en bedre helbreds status end den generelle danske befolkning. Vi fandt desuden en øget dødelighed blandt patienter med SCC af kardiovaskulære sygdomme, kronisk lungesygdomme, genitale sygdomme og akutte infektioner.

På baggrund af resultaterne fra alle 4 studier, synes kronisk sygdom som risiko- og prognostisk faktor at være meget forskellig for BCC og SCC, hvorfor man bør studere de to cancertyper separat. Dog fandt vi i sidste studie, at både patienter med BCC og SCC havde en øget årsagsspecifik dødelighed af anden cancersygdom, hvilket antyder en fælles abnorm tilstand i immun systemet, der gør at NMSC og andre cancere kan udvikle sig.

Vores studier har belyst de fejlkilder, der er forbundet med at lave forskning på NMSC. Hvis der tages hensyn til disse, kan observationelle studier bidrage med betydelig viden om denne sygdom. Derfor håber vi i fremtiden at kunne etablere en database med komplet registrering af alle NMSC tilfælde og vha. denne udføre større studier og undersøge mere komplekse risikofaktorer til - og sygdomsudfald af NMSC.

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