The use of new and existing data sources in non-melanoma skin cancer research

PhD dissertation

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Preface

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

The work leading to 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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- I. Lamberg AL, Jensen AØ, Olesen AB, and Sørensen HT. Hip fracture and risk of nonmelanoma skin cancer: A Danish population-based study.
- II. Lamberg AL, Cronin-Fenton DP, Sølvsten H, and Olesen AB. The Danish Regional Non-Melanoma Skin Cancer Dermatology Database: structure, content and promise.
- III. Lamberg AL, Cronin-Fenton D, and Olesen AB. Registration in the Danish Regional Non-melanoma Skin Cancer Dermatology Database: Completeness of registration of non-melanoma skin cancer and accuracy of key variables in the database. Clinical Epidemiology. 2010.
- IV. Lamberg AL, Olesen AB, Sølvsten H, and Cronin-Fenton DP. Who attends follow-up after treatment of basal cell carcinoma? A Danish cohort study.

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ABBREVIATIONS

BCC: Basal cell carcinoma SCC: Squamous cell carcinoma NMSC: Non-melanoma skin cancer IARC: International Agency for Research on Cancer CRS: The Danish Civil Registration System DCR: The Danish Cancer Registry DNPR: The Danish National Patient Registry DPR: The Danish Pathology Registry IDA: The Integrated Database for Labor Market Research ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification CPT: Treatment using current procedural terminology PPV: Positive predictive value NPV: Negative predictive value SE: Sensitivity SP: Specificity N: Numbers CI: Confidence interval

Introduction

Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are frequently described as nonmelanoma skin cancers (NMSCs) and comprise 95% of all NMSCs¹. However, the term NMSC also includes other forms of skin cancers that do not involve melanocytes². A more correct term to describe BCCs and SCCs is keratinocyte carcinomas². However, the term NMSC will be used in this thesis to describe BCCs and SCCs, as this is the most commonly used term.

NMSC is the most common cancer in the Caucasian population and is an important challenge in terms of public health management. However, a lack of detailed and complete epidemiological data on NMSC hampers better understanding of the epidemiology and public health management of NMSC. To improve the prevention and treatment of NMSC, we need better understanding of the disease, including its risk, prognosis, and treatment.

This thesis concerns the use of existing data sources in NMSC research, and the development, validation and use of a new clinical database for BCC, SCC, in situ Bowen's disease, and the benign keratoacanthoma. Bowen's disease and keratoacanthoma are included in the clinical database because Bowen's disease is a late precursor for SCC, and keratoacanthoma is a benign lesion histologically similar to SCC. However, this thesis concerns BCC and SCC.

Basal cell carcinoma

BCC arises from cells of the skin that reside in the basal layer of the epidermis or epithelial structure of the adnexa². Metastasis of BCC is rare^{2;3}, but it can spread via lymphatic paths to regional nodes and/or via the bloodstream to the head and neck^{2;3}. BCCs have three well-recognized growth patterns that can be recognized both clinically and histologically: nodular, superficial, and morpheic². The superficial and morpheic types have characteristic histopathological pictures that vary little from lesion to lesion². However, nodular BCCs may show many different histopathological variants².

Nodular BCC (nodulo-ulcerative): Sixty percent of BCCs are nodular and most commonly localized on sites chronically exposed to the sun, including the head and neck^{2;4}. The lesion is a red, well-defined nodule with a translucent appearance and overlying telangiectasia. Ulcerations may occur, especially as the tumor grows. Many nodular BCCs show secondary changes or unusual features, and some of these findings may correlate with a more aggressive biological behavior (e.g., squamous differentiation, stromal sclerosis, or a diffuse infiltrative pattern)².

Superficial BCC: Superficial BCC is also a very common variant of the cancer and commonly found on areas exposed to intermittent sun exposure, such as the trunk and extremities^{2;4}. Typically, the BCC lesion is flat and pink or red, and patients may present with multiple lesions².

Morpheic BCC: The morpheic type is the least common, and most aggressive, form of BCC. The lesion is typically indurated, sclerotic, and ivory in color, sometimes with overlying teleangiectasia. The growth pattern is diffuse, and the disease can spread subclinically with poorly defined tumor margins. Therefore, morpheaform BCC has a high recurrence rate after treatment^{2,5}.

Squamous cell carcinoma

SCC can develop in all tissues lined by squamous epithelia, including the skin, mouth, esophagus, and vagina. However, the biology of cutaneous SCC differs from SCCs that arise in other regions, with a relatively indolent behavior and infrequent metastases $(2-6\%)^{2;6}$. Cutaneous SCC metastasizes primarily through the lymphatics to regional nodes, most often involving the parotid and cervical nodes. Cutaneous SCCs arise in skin chronically exposed to the sun; the most common anatomic site for SCC is the head and neck region^{2;6;7}.

Actinic keratosis and Bowen's disease are precursors of SCC, showing similar keratinocyte atypia². The common clinical presentation of invasive SCC is an erythematous keratotic papule or nodule arising within a background of sun damaged skin. The lesion slowly or rapidly enlarges to become more nodular².

Bowen's disease

Bowen's disease is a precursor of SCC and regarded as *in situ* SCC with atypical epidermal keratinocytes. Bowen's disease is most often a slightly scaly, discrete, erythematous plaque with a sharp, but often irregular, border².

Keratoacanthoma

Keratoacanthoma is also known as a 'self-healing SCC'. Histologically, the pattern resembles a typical SCC, but clinically the keratoacanthoma differs from typical SCC. The typical keratoacanthoma is a rapidly enlarging papule that evolves into a sharply circumscribed crateriform nodule with a keratotic core over a period of few weeks, and then may resolve slowly over months to leave an atrophic scar^{2;8}.

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The epidemiology of NMSC

Incidence

NMSC is the most common cancer among Caucasians. Unlike other cancers, the incidence of NMSC is not well documented⁹. Data on NMSCs are not routinely collected by many cancer registries worldwide, including the US Surveillance Epidemiology and End Results (SEER) Program. In some cancer registries only SCCs are recorded⁹⁻¹¹, whereas BCC and SCC are registered as one entity in other registries⁹⁻¹¹. A common factor among all of the registries that record NMSC, including the Danish Cancer Registry (DCR), is incomplete registration^{9;12-18}.

In North America and Australia, an attempt to estimate incidence has been made by conducting large population-based surveys, and medical record and pathology record reviews^{7;19-21}. In North America, the incidence of NMSC has also been estimated using data from Medicare, a government-funded health plan available to citizens aged 65 years and older²².

The incidence of NMSC increases with age^{7;20;23} and varies according to latitude due to the impact of sunlight exposure on its etiology. Finland reports some of the lowest incidence rates and Australia the highest rates^{21;24}. The estimated incidence is provided in Table 1.

BCC is more common than SCC. The ratio depends on latitude and is notably reduced in Australia and increased in Denmark, where the ratio of BCC to SCC is 9:1 (Table 1). The incidence of NMSC is increasing worldwide with the most pronounced increase in Australia, where fair-skinned people live in the closest proximity to the equator. This increase translates into an annual increase in incidence as high as 3-10% for both BCC and SCC^{7;20;23;25}. In Denmark, an almost three-fold increase in the incidence has been seen since the 1970s (Figure 1), and a steep increase has been seen in women younger than 40 years of age²⁶.

Figure 1 Age-standardized incidence rates of NMSC per 100,000 persons per year in Denmark from 1943 to 2003 (World standard population)²³.



Table 1 Age-standardized incidence rates for BCC and SCC in Europe, North America, and Australia.

	Study periodIncidence rate of BCC per 100,000Incidence rate of SCC per 100,000MaleFemale		Data source	Stan- dard popula- tion			
Europe							
Denmark ²⁶	2007	91	97	19	12	Cancer and Pathology Registry	World
Scotland ²⁷	2001-2003	61	47	24	9	Cancer Registry	World
Northern Ireland ²⁸	1993-2002	94	72	46	23	Cancer Registry	World
Finland ²⁴	1991-1995	49	45	7	4	Cancer Registry	World
Switzerland, Canton of Vaud ²⁹	1995-1998	75	67	28	17	Cancer Registry	World
North America							
New Hampshire ²⁰	1993-1994	310	166	97	32	Population Registry	US, 1970
Arizona ⁷	1996	936	497	271	112	Survey	World
New Mexico ¹⁹	1998-1999	930	486	356	150	Cancer Registry	US, 2000
Australia							
North region($<29^{\circ}$ S) ²¹ Central region (29°S-37°S) ²¹ South region ($>37^{\circ}$ S) ²¹	2002	2145 1088 646	1259 843 462	1240 473 306	429 400 171	Household Study	World
Nambour, Queensland ³⁰	1985-1992	2074	1579	1773	1610	Household Study	World

Danish NMSC data sources

Denmark has, compared to most countries, an extensive registration of NMSC. NMSC patients may be identified in four population-based data sources:

The Danish Cancer Registry (DCR)

The DCR contains nationwide information on primary cases of cancer since 1943, including information on primary cases of NMSC³¹. Registration is done according to the rules of the International Agency for Research on Cancer (IARC)³². Multiple (synchronous or non-synchronous) primary tumors with the same histology are only registered once in the DCR. In other words, patients with multiple BCCs diagnosed the same day or with years in between are counted only once for the estimation of BCC incidence. If a SCC is also diagnosed in this patient, the SCC would be counted as a new incident.

DCR files include information on cancer type, site, and morphology. In the DCR, tumors have been coded according to the 10th revision of the International Classification of Diseases (ICD-10) since 1978. In addition, tumors are coded according to the third version of the International Classification of Diseases for Oncology (ICD-O-3), which includes a four-digit code for tumor morphology³¹.

The DCR has shown high validity and completeness of cancer registration³¹; however, BCC is estimated to be incompletely registered^{16-18;33}.

The Danish Pathology Registry (DPR)

The DPR contains information on all histological examinations performed in Denmark. Since 2005, reporting to the DPR has been mandatory for both privately and publicly employed pathologists. The registry includes information on the treating and diagnostic department, the date of the pathology test, and the associated histological diagnoses. All diagnoses are coded according to systematized Nomenclature of Medicine (SNOMED)³⁴.

It is difficult to assess the correctness of the data in the DPR (i.e. the accuracy of the pathology conclusion or diagnosis), because the pathology examination is considered the gold standard³⁴.

Danish National Patient Registry (DNPR)

The DNPR, which was established in 1977 and includes each hospital inpatient admission since 1977 and outpatient and emergency room visits since 1995³⁵. The DNPR registers the patient's civil registration number, dates of admission and discharge, and up to 20 discharge diagnoses classified according to the International Classification of Diseases (ICD), using the 8th revision until the end of 1993 and 10th revision thereafter.

However, the majority of NMSC tumors are treated in office based settings and not in hospital settings³⁶, and the DNPR only have data on patients treated in a hospital setting.

The Gerda Frentz cohort

In 1995, Professor Gerda Frentz established a nationwide NMSC cohort, the "Gerda Frentz cohort"³⁷, by prospectively recording all patients with NMSC diagnosed by Danish dermatologists in that year; both first primaries and subsequent new primaries were included. Two sources were used to establish the cohort. The first source was recordings made by dermatologists in office based settings and hospital outpatient clinics. The following clinical data were registered: tumor site, size and clinical diagnosis, treatment modality and history of NMSCs. The second source comprised all patients with a histological review of suspected NMSCs sent to a pathologist. These data included biopsies diagnosed as NMSC. Histological data on these tumors included the final histological diagnosis, the type of referring clinic and, if appropriate, details on the tumor growth pattern, differentiation and margins of excision.

Methodological problems in studying NMSC

Observational studies using administrative data are suitable for studying risk factors and the prognosis of NMSC. Observational studies are usually based on analytical methods, such as cohort or case-control study designs. The use of administrative databases, such as the DCR, DPR and DNPR, offers a number of advantages: 1) large sample size, ensuring precise risk estimates and generalizability; 2) low cost due to the use of an existing database with which no new data needs to be collected; 3) prospective collection independent of the outcomes in the study, reducing both selection and information bias; and 4) the timely and early dissemination of information on outcome.

However, it is important to be aware of the limitations of the administrative databases. The data collection and quality of the data entered into the databases are not controlled by the researcher. In order to ensure data quality, a simple and uniform registration system with computerized checks is important.

The DPR, containing all histological examinations, is a valuable data source, which can be used in the evaluation of data quality of other data sources. Continuous exchange of information between the DPR and the DCR is done in order to improve accurate and complete cancer registration in Denmark. Using data from the DPR, the DCR estimates the incomplete registration of primary BCC tumors to be as high as 50%³³. The incomplete registration may lead to bias if unregistered NMSC patients differ according to risk factors and outcome variables.

The public health importance of NMSC is therefore not appropriately reflected by the populationbased cancer registries including the DCR, not only because of the incompleteness of registration, but also because multiple (synchronous or non-synchronous) primary tumors with the same histology are only registered once, and approximately 44% of NMSC patients develop subsequent NMSC(s) within 2 years³⁸. New accurate data are needed for effective public health monitoring and intervention¹.

Another limitation of the existing data source is lack of detailed clinical data and detailed outcome measures. This absence of detailed data limits the possibilities for investigating risk and prognosis, because in contrast to other cancer forms, the mortality of NMSC is low, and more complex health outcomes are of interest, i.e. incidence of new subsequent tumors, recurrence, cosmetic result or quality of life. The Gerda Frentz cohort is an example of a more detailed registration of all NMSCs³⁷. However, the registration was done only for one year and no outcome measures (e.g., the recurrence rate or cosmetic result) were included in the registration.

Determining treatment efficacy (i.e., the recurrence rate or cosmetic result under ideal conditions) can, in theory, be best studied in a randomized controlled trial³⁹. Nevertheless, randomized clinical trials have several limitations; trials often reflect the efficacy of a specific treatment performed at a specific hospital, or even by a specific physician, on a specific type of patient. Therefore, these studies may often be influenced by possible performance bias, selection bias, and impaired generalizability³⁹.

For practical purposes, effectiveness (i.e., the extent to which NMSC treatment fulfills its objectives in routine clinical settings) may be a more relevant measure than efficacy. Observational studies play a central role in the assessment of effectiveness because these studies can be based on information from everyday clinical practice. A specific category of observational studies is retrospective case series, and they have been widely used in assessing the effectiveness of NMSC treatments. However, these studies are often limited by the lack of generalizability and the absence of a reference group.

Detailed data on NMSC and the treatment of NMSC in everyday clinical practice are important for surveillance, predicting prognosis, improvements in the quality of care and treatment, and for research purposes^{1;40}. Such data can only be obtained from properly designed clinical databases, which are an attractive source for epidemiological research^{40;41}, and population-based clinical databases that record information on treatment, prognostic factors, and outcome can be important tools for monitoring NMSC treatment. The use of a clinical database in NMSC research has the same advantages as other administrative data sources: 1) the timely and early dissemination of information on the outcome of NMSC treatment; 2) large sample size that ensures precision and generalizability; and 3) the prospective information in clinical databases is independent of the outcomes in the study of interest, reducing both selection and information bias.

In order to obtain detailed clinical data on NMSC on all NMSC tumors, both first and subsequent tumors, a clinical database was developed as a part of this PhD, the Danish Regional NMSC Dermatology Database (NMSC database). The NMSC database contains detailed clinical data including information on treatment, prognostic factors, and outcome on all NMSCs and not only first primary NMSC⁴².

Existing clinical NMSC databases and validation of the data sources (Studies II & III)

Above, we described the limitation of the existing Danish administrative data sources, which routinely register NMSC. We searched Medline to identify articles using population-based NMSC data sources that include detailed data on treatment, prognostic factors, and outcome using the following terms:

 ("Skin Neoplasms"[Mesh] AND ("Carcinoma, Basal Cell"[Mesh] OR "Carcinoma, Squamous Cell"[Mesh])) AND ("Registries"[Mesh] OR "Database "[Publication Type]) To ensure that NMSC data sources that include information on treatment outcome were included in our search, we also searched Medline with the following terms:

 ("Skin Neoplasms"[Mesh] AND ("Carcinoma, Basal Cell"[Mesh] OR "Carcinoma, Squamous Cell"[Mesh])) AND ("Treatment Outcome"[Mesh] OR "Outcome Assessment (Health Care)"[Mesh])

Only articles using population-based data sources within the last two decades were included. The reference lists of selected publications were searched for other relevant articles. If the same data source was used in multiple articles, only one article was included (Table 2).

Our literature search revealed only one NMSC data source, the Cutaneous Cancer Registry in Trentino, Italy, which includes detailed information on prognostic factors, treatment, and follow-up data⁴³. However, no details on the follow-up data were provided in the article, and data were obtained by interviewing the patients, who were invited to a free clinical follow-up⁴³.

Several surveys have been conducted to obtain information on the incidence of NMSC, as well as detailed information on, for example, age, gender, and size and anatomical location of the tumor^{7;19;20;44-47}. However, none of the studies have included outcome data (e.g., recurrence, complications, or cosmetic result).

In the United States, Medicare compiles claims databases of its enrollees, and it is possible to obtain information on diagnosis, treatment, and the cost of treatment^{22;36;48-51}. However, only patients aged over 65 years are included. Private insurers and health maintenance organizations (HMO) also maintain claims databases with information on the diagnosis and treatment of NMSC. The HMO Cancer Research Network combines data from 14 HMOs, such as Kaiser Permanente and Harvard Pilgrim Health Care⁴⁹. The registration of NMSC patients in one of the HMOs, the Henry Ford Health System, has been validated against medical records and found to have a high positive predictive value (PPV: 97-98%)⁴⁸. In contrast, the PPV of claims data in another health system administrative database was low. However, if both the diagnosis and treatment codes were used in the identification of the NMSC patients, the PPV was higher⁴⁸. Claims data have been used to estimate the prevalence, treatment, and cost of treatment of NMSC. However, the limitations of using such claims data include selection bias due to selected study populations and the variable quality of the clinical data⁵²

Table 2 Studies using population-based NMSC data sources that include detailed clinical data on treatment, prognostic factors, and outcome.

Outcome Validation of data	variables source	None Not stated in the article	NoneThe Danish Cancer Registry is known to be incomplete ³³ ; the Danish National Pathology Registry contains all pathology examinations performed in Denmark ³⁴	Follow-up Not stated in the article information (not specified in the article)	None 85% completeness Reabstraction of records indicated 97.5% concurrence for all registry information	None Not stated in the article	None Nearly all diagnoses are
Treatment and prognostic	variables	Gender, age, histological type, typography, skin cancer history, and treatment	Gender, age, histological type, topography, and morphology	Tumor-related data: anatomical site, clinical and histological diagnoses, date of diagnosis, state of surgical edges, and presence of associate lesions. Patient-related data: name, date of birth, gender, phenotypical characteristics, history of early sunburn, previous radiation therapy or trauma at the site of the lesion, profession, family history, concurrent diseases, and smoking and drinking habits.	Histological type, anatomic site, diagnosis date, age, gender, referring physician, and laboratory at which the pathology diagnosis was made	Diagnosis date, histological type, stage, anatomic site, birth date, ethnicity, and gender	Diagnosis, age, gender, anatomical
Setting/data source		The Gerda Frentz cohort	Incident cases of BCC and SCC generated from the Danish Cancer Registry and the Danish National Pathology Registry	Incident cases of skin cancer identified from records at three pathology departments; incident cases of NMSC were interviewed at a free clinical follow-up	"The Southeastern Arizona Skin cancer Registry" registering skin cancer from 1985-1996	Cases identified from pathology records, biopsy logs, and billing records	"Cancer Treatment and Outcome
Number		10,749	178,386 incident NMSCs	2,868 incident cases of skin cancer with a total of 3,435 tumors	100,266 NMSCs	160 SCCs, 1,211 BCCs	490 NMSCs
Study	period	1995	1978- 2007	1992- 1998	1985- 1989, 1993 and 1996	1993- 1994	1998
Location		Denmark	Denmark	Trentino, Italy	Southeastern Arizona, US	New Hampshire, US	South Wales,
Authors,	year	Jensen ⁴⁶ , 2007	Birch- Johansen ²⁶ , 2010	Boi ³³ , 2003	Harris ⁷ , 2001	Karagas ²⁰ , 1999	Holmes ⁵⁴ ,

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				from pathology departments with cross-correlation of cancer diagnosis from oncology, dermatology, and other specialists' outpatient letters over a 6-month period			for tumors with only a clinical diagnosis
Staples ²¹ , 2006	Australia	2002	817 NMSC patients	Face to face interview conducted in households within selected clusters.	Gender, histological type, anatomical site, skin reaction to sunlight, age, latitude of residence, region at birth, income, and educational level	None	The diagnosis of all 817 NMSC patients were confirmed were confirmed with the treatment provider.
Athas ¹⁹ , 2003	North central New Mexico, US	1998- 1999	4,194 NMSCs	Data on new primary NMSC were obtained from records from pathology lab, dermatologists, dermatopathologists, plastic surgeons, radiologists, and general surgeons	Gender, histological type, anatomical site skin, ethnicity, residence address at diagnosis	None	Not stated in the article
Rogers ²² , 2010	ns	2006	Patients >65 years of age	Medicare claims data and The National Ambulatory Medical Care Survey	Skin cancer patients can be identified by diagnosis using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) Treatment using current procedural terminology (CPT)	Not stated in the article	Not stated in the article
Eide ⁴⁸ , 2010	Southeastern Michigan, US	2007	11,742 NMSC patients	NMSC patients were identified in health maintenance organization database (HMO) claims and all- payers claims in a health system administrative database, both owned by Henry Ford Medical group.	Diagnosis using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) Treatment using current procedural terminology (CPT)	None	All-payers claim data were validated by the review of 965 patient charts. Positive predictive value (PPV) of ICD-9-CM-identified patients=47%, PPV of CPT-identified patients=73%, PPV using both codes=95% HMO claims data were validated by the review of 1,116 medical records PPV of ICD-9-CM-identified patients=97%, PPV of CPT- identified patients=98%,

Not stated in the article	Not stated in the article	Random subsample of 40 BCCs was identified in the database, 93% were confirmed as BCCs by hospital letter and/or pathology report	Pathology reports were compared with the Queensland Cancer Registry	Not stated in the article	Not stated in the article	Not stated in the article
None	None	None	None	None	None	None
Gender, age, number of BCCs, diagnosis	Gender, age, location, number of BCCs, size, BCC clinical subtype	A database of anonymised clinical records for over 4 million patients in the UK: All variables not stated in the article	Histopathological classification, anatomical site	Age, gender, anatomical site, metastasis	Numbers of skin cancers, gender, age, diagnosis, anatomical site, hair color, nevi, solar damage, freckling, occupation, sun habits	Diagnosis, Gender, age, anatomical site
BCC diagnosed by dermatologists in Barcelonès.	BCC patient seen by randomly selected dermatologists in 4 non- consecutive weeks	The Health Improvement Network (THIN)	All excised and histologically verified BCCs in Townville	Medical record review of all SCC identified through diagnostic, procedure and pathologic specimen recorded at the Mayo Clinic or in the Rochester Epidemiology project.	The subject were randomly selected from the Nambour population (aged 20-69years old) and followed through postal survey and whole body skin examination, and pathology records	Skin cancers diagnosed by a network of physicians covering the majority of the residential population reported by the physician and through pathology reports
936 BCC patients	1,655 BCCs	11,113 BCC patients	5,044 BCC patients	511 SCCs	1,675 persons	730 BCCs, 159 SCCs, 107 malignant melanomas
2006- 2007	2004	1996- 2003	1997- 1999	1984- 1992	1986- 2006	1998- 2003
Barcelones Nord county, Spain	France	UK	Townsville, Australia	Olmsted County, US	Nambour, Australia	Northrhine- Westphalia
Bielsa ⁵⁵ , 2009	Bernard ⁵⁶ , 2007	Bath- Hextall ⁵⁷ , 2007	Raasch ⁵⁸ , 2006	Gray ⁴⁴ , 1997	Green ³⁰ , 1996 Rishmond- Sinclair ⁵⁹ , 2009	Stang ⁶⁰ , 2007

Risk factors

Ultraviolet radiation and skin phenotype

The primary risk factor for both BCC and SCC is sun exposure⁶¹. Ultraviolet (UV) rays, including UVB, UVA, and UVC, can induce DNA damage in normal skin cells. UVB is mutagenic and immunosuppressive, leading to photo-carcinogenesis in skin cancer². UVA is also carcinogenic, but not as efficient, presumably by orders of magnitude². UVC is absorbed by the ozone layer and does not reach the Earth's surface.

Different sun exposure habits are thought to impact skin cancer risk. Intermittent high-dose sun exposure is thought to be the main risk factor for BCC⁶²⁻⁶⁵, whereas cumulative sun exposure is thought to be the main risk factor for SCC^{64;66}. However, the skin's reaction to sun exposure also impacts skin cancer risk. Skin that burns easily or tans poorly are risk factors⁶⁷⁻⁶⁹ and correspond to "Fitzpatrick" skin phenotypes I and II (fair and/or easily sunburned). In 1975, Fitzpatrick created a skin typing system based on a person's erythema and tanning reaction to their first sun exposure in early summer⁷⁰. However, self-reported burning tendency and tanning ability have limitations, and the classification has been shown to be an unreliable measure of the first skin reaction^{71;72}. A Danish study suggested that people seem to refer to sun sensitivity after multiple exposures to the sun rather than a single sun dose⁷³. The classification is simple and easy to use though, and still the most used classification of skin type.

Chemicals and smoking

Exposure to ionizing radiation, either iatrogenic (treatment for acne, tinea capitis, cancer), occupational (uranium in mines), or accidental (atomic bomb explosion), elevates the risk for BCC three-fold⁷⁴. For SCC, an association with ionizing radiation has only been found in individuals prone to sunburn with sun exposure⁷⁴.

Occupational exposure to polycyclic aromatic hydrocarbons, including mineral oil, shale oil, coal tar, and soot, has been shown to elevate the risk of NMSC, especially SCC^{75;76}. Exposure to arsenic in drinking water, by occupational exposure, or in psoriasis treatment (formerly used) can cause Bowen's disease, SCC, and superficial BCC^{2;77}. However, a Danish study suggested that the low dose of arsenic in Danish drinking water is associated with a reduced risk of skin cancer⁷⁸.

Smoking has been reported to double the risk of SCC in a dose-dependent manner⁷⁹. However, no clear relationship has been found between smoking and the risk of BCC⁷⁹.

Immunosuppression

Patients with impaired immune function, such as those receiving immunosuppressive drugs or those with hematological cancers, have an increased risk of NMSC⁸⁰⁻⁸², and some SCCs are associated with human papillomavirus infection². Organ transplant recipients have a markedly increased incidence of NMSC, especially SCCs^{83;84}. The incidence of BCC is increased 4-19 times, whereas the incidence of SCC is increased 40-250 times than in the general population. Risk factors include skin type, sun exposure, and the degree and duration of immunosuppression^{83;84}. Research has also indicated that a history of chronic disease increases the risk of SCC, but no substantial increase in the risk of BCC was found.

Genetic disorders

Genetic disorders can predispose an individual to cutaneous malignancies. The two best known disorders are basal cell nevus syndrome (BCNS) and xeroderma pigmentosum (XP)². BCNS is an autosomal dominant disorder affecting a tumor suppressor gene, and XP is an autosomal recessive disorder in which impaired repair of UV-induced damage results in DNA damage².

Skin cancer prognosis

Several factors influence the outcome of a disease (Figure 2). The simplest method to assess health outcome in a particular population, such as NMSC patients in this case, is by estimating associated morbidity and mortality. More complex health indicators are discomfort, disability, and dissatisfaction (quality of life)⁸⁵.

Mortality from BCC is very low⁸⁶, and mortality from SCC is higher than that of BCC but still low. In Denmark, the annual reported mortality rate is 0.4 per 100,000 NMSC patients²³, but inaccuracies in the death certificate information may overestimate the actual mortality⁸⁷. Prognostic factors for NMSC can be divided into NMSC-related factors, treatment-related factors, and patientrelated factors (Figure 2).



(recovery, chronicity, disability, or death)

Figure 2 Factors that may determine the prognosis of patients with NMSC⁸⁸.

NMSC-related factors influencing prognosis include the type, size, and location of NMSC, failure of previous treatment, and histological differentiation^{6;89-91}. High risk precursors for the recurrence and metastasis for BCC are location in the central face or ear, size >2 cm, failure of previous treatment, morpheic BCC, and BCC with a histopathological growth pattern (e.g., squamous differentiation or infiltrative growth pattern) correlated with a more aggressive biological behavior. High risk precursors for SCC are localization on the lip, ear, and non-sun-exposed sites (e.g., perineum, sacrum, sole of foot), increasing size and depth, failure of previous treatment, and histologically poor to moderate differentiation^{6;91;92}.

Treatment-related factors have a significant impact on prognosis. The aim of treatment is complete removal of a tumor in a manner likely to result in a cosmetic outcome that will be acceptable to the patient⁹⁰. A wide range of treatments are used in the management of BCC, with surgery and radiotherapy regarded as the most effective treatments⁹³. However, for tumors that are considered to be less aggressive based on the prognostic factors described above, an optimal cosmetic result often receives higher priority than total removal⁹⁰. Selecting appropriate tumors for less aggressive treatment is essential for the prognosis^{90;91}. Similarly, the treating clinician's management and experience is important for the prognosis⁹⁴.

Patient-related factors may also influence NMSC prognosis. Higher mortality is seen with increasing age, male gender, and in the Caucasian population⁹⁵. The patient's physical performance, especially immune function, is important for the prognosis. Organ-transplant recipients have a high risk of recurrence and NMSC-related death^{83;84}. In general, chronic comorbidity is also known to

have an impact on the prognosis of most diseases⁹⁶. The patient's lifestyle and adherence may also impact the prognosis; smoking can impact wound healing after treatment⁹⁷. Some patients may ignore a slow growing tumor, resulting in delayed diagnosis, which is associated with a worse prognosis. Patient preference can also influence outcome. Patients may refuse to undergo the optimal tumor treatment for cosmetic concerns, which may result in a worse prognosis due to an increased risk of recurrence.

Sunlight and vitamin D

In humans, vitamin D is mainly obtained through exposure of the skin to direct sunlight⁹⁸. Sunlight causes oncogenic mutations in the skin leading to skin cancers, including BCC, SCC, and malignant melanoma (MM)⁹⁹. Regular, intermittent exposure of unprotected skin to the sun, which is associated with BCC development⁶², is the best way to increase vitamin D accumulation⁹⁸. In contrast, prolonged, cumulative exposure of unprotected skin to the sun, which is associated with SCC development⁶⁶, may not lead to more vitamin D accumulation because the amount of previtamin D that can form in the skin is limited, and the ability to produce pre-vitamin D is dependent on skin pigmentation (i.e. the more pigmentation the lower the amount of pre-vitamin D synthesised per dose of UVB)^{98;100}. In addition, vitamin D is itself photolabile and can be broken down by sunlight^{101;102}.

Recently, much attention has been given to the health effects of vitamin D status and vitamin D supplementation¹⁰³. Insufficient vitamin D may affect a wide range of conditions, such as cancer, cardiovascular disease, glucose intolerance, and diabetes ¹⁰⁴⁻¹⁰⁷. Two previous Danish studies reported better survival among BCC patients compared with the general population^{108;109}. Jensen *et al* reported reduced cause-specific mortality from cardiovascular disease, chronic pulmonary disease, and diabetes mellitus among patients with BCC, the diseases for which vitamin D is suggested to be protective ^{104;108}. Patients with BCC may, through intermittent sun exposure, have adequate vitamin D levels with beneficial health effects.

Hip fracture and NMSC

Vitamin D is essential for bone mineralization because of its role in maintaining adequate levels of serum calcium and phosphorus¹¹⁰. Vitamin D deficiency precipitates and exacerbates osteoporosis and muscle weakness, factors that enhance the risk of fractures¹¹¹⁻¹¹⁴. If BCC patients have higher vitamin D levels than the background population due to sun exposure, they may have a lower risk of hip fracture than the background population.

Existing literature on the link between fractures and NMSC (Study I)

We searched Medline to identify existing literature on the association between NMSC and fracture risk using the following free text search and Mesh term search:

- "Fractures, Bone"[Mesh] AND "Skin Neoplasms"[Mesh] AND ("Neoplasms, Basal Cell"[Mesh] OR "Neoplasms, Squamous Cell"[Mesh])
- "Fracture" AND "non-melanoma skin cancer"

We limited our search to studies in humans that were published in English or Danish. In addition, the reference lists of selected publications were searched for other relevant articles.

To our knowledge only one study investigated this association; a Tasmanian study investigated the association between NMSC and hip fracture risk using NMSC as a biomarker for sun exposure¹¹⁵. A 31% lower incidence of prior NMSC was reported in a cohort of fracture patients using sex-, age-, and calendar year-specific cancer incidence rates in southern Tasmania as a reference¹¹⁵. However, the study did not consider important potential confounding factors, such as chronic diseases and socioeconomic status (SES), associated with the risk of hip fracture and NMSC.

In addition, we searched Medline to identify studies that have investigated serum vitamin D levels in NMSC patients. We used the following free text search and Mesh-term search:

- "Vitamin D"[Mesh]AND "Skin Neoplasms"[Mesh] AND ("Neoplasms, Basal Cell"[Mesh]
 OR "Neoplasms, Squamous Cell"[Mesh])
- "Vitamin D" AND "non-melanoma skin cancer"
- "Serum vitamin d" and "skin cancer"
- "Vitamin d level" and "skin cancer"

We limited our search to studies in humans that were published in English or Danish. In addition, the reference lists of selected publications were searched for other relevant articles.

In a nested case-control study, serum 25(OH)D levels were measured in 220 BCC patients and 220 controls¹¹⁶. Blood samples were collected 4 to 21 years before the BCC diagnosis or the corresponding date for the controls. The findings suggested that higher pre-diagnostic serum 25(OH)D levels may be associated with an increased risk of subsequent BCC¹¹⁶. In contrast, a nested case-control study of elderly men (>65 years of age) found an inverse association between serum 25(OH)D levels and self-reported NMSC¹¹⁷. Serum 25(OH)D levels were measured at

baseline. Information on participants' NMSC history was collected at baseline and at a 5-year follow-up visit. However, the findings may be biased due to a change in sun exposure patterns after the NMSC diagnosis. Vitamin D levels change with changing sun exposure or vitamin D intake, and measurement of one serum vitamin D level is not representative for lifelong exposure to vitamin D.

NMSC management

A wide range of different treatments are used in the management of NMSC¹¹⁸, and guidelines have been published on their appropriate use^{90;91;118-121}. The aim of SCC treatment is complete removal⁹¹, whereas the aim in BCC is usually to eradicate the tumor in a manner that is likely to result in a cosmetic outcome that will be acceptable to the patients⁹⁰.

In the treatment of BCCs and SCCs with a low risk of recurrence (as outlined in the "NMSC prognosis" section), several treatments may be applied according to guidelines^{90;91;118-121}. However, knowledge on the efficacy of the treatment modalities used for SCC and BCC is mainly based on outcomes from selected patient groups in a hospital setting, and few randomized controlled studies have been conducted^{90;91;93}.

Care for NMSC is provided at hospitals, outpatient clinics, ambulatory surgical centers, and physician offices. NMSC is most often treated by dermatologists, though general surgeons, plastic surgeons, otolaryngologists, oncologists, and family physicians may also treat the condition^{122;123}. However, data on management in routine clinical settings is sparse.

Existing literature on the management of NMSC (Study II)

We searched Medline to identify articles on the management of NMSC in routine clinical practice using the following terms:

 "Skin Neoplasms"[Mesh] AND ("Neoplasms, Basal Cell"[Mesh] OR "Neoplasms, Squamous Cell"[Mesh]) AND ("Patient Care Management"[Mesh] OR ("Therapeutics/economics"[Mesh] OR "Therapeutics/statistics and numerical data"[Mesh] OR "Therapeutics/trends"[Mesh] OR "Therapeutics/utilization"[Mesh])) We limited our search to population-based studies in humans that were published in English or Danish. In addition, the reference lists of selected publications were searched for other relevant articles (Table 3).

Data from a Danish dermatology clinic has shown that curettage with cautery is the most commonly used treatment in the routine clinical practice of the clinic^{124;125}. Although these findings were based on a single dermatology clinic, and was not population–based, the data are concordant with unpublished data from the Gerda Frentz Cohort³⁷. US Medicare data have shown that 50% to 80% of all NMSCs are treated by dermatologists, and the majority of patients are treated in an office-based setting^{36;50;51}. A study of the in-hospital management of skin cancer in Germany reported that the majority of NMSC hospitalizations are in dermatology departments¹²⁶.

The management of NMSC differs between countries. A UK study reported that the preferred treatments of BCC by dermatologists are excision (58%), curettage with cautery (24%), cryotherapy (8%), and radiotherapy (8%)¹²⁷, and a study from Scotland reported that 83% were treated with excision by consulting dermatologists, whereas only 9% with curettage with cautery¹²⁸. An US study reported differences between treatments in a private dermatology clinic and a Veterans Affairs clinic¹²⁹. Curettage with cautery was used in 23% of the cases in the private clinic and 19% of the cases in the Veterans Affairs clinic, whereas excision was used in 25% of the private clinic cases and 48% of the Veterans Affairs cases¹²⁹.

Authors,	Study	Study aim	Setting	Study	Number	Results in relation to
country,	period	-	-	design		treatment pattern
vear	-			U U		-
Manternach ⁵ ¹ , US, 2003	1998- 1999	To determine how frequently different specialists use different types of surgical treatments	Medicare claims data	Cross sectional	1,986,159 surgical episodes of NMSC care	82% of all NMSC treatments were performed by dermatologists Dermatologists performed: 95% of all destructions; 56% of all excisions; 100% of all Mohs surgeries; 70% of more complicated repairs (e.g., flap and graft closure); 90% of all biopsies
Smith ¹²³ , US, 1998	1993- 1994	To determine the characteristics of office-based physician visits for actinic keratosis and NMSC	A National Medical Care Survey Data (NAMSC)	Cross sectional	6,261,000 office-based visits with the diagnosis of NMSC	80% of all NMSC episodes were performed in dermatology clinics, 4.3% in family practice, 7.3% in plastic surgery, 3.1% in internal medicine, 1.0% otolaryngology, 0.6 % in other specialties
Joseph, US ⁵⁰ , 2001	1994- 1995	Prevalence and cost of treatment	5% sample of Medicare claims data	Cross sectional	789,260 patients > 65 years of age covered by Medicare treated for NMSC	Specialists providing NMSC treatment: 62% dermatology; 12% radiation oncology; 5% general surgery; 5% plastic surgery; 5% diagnostic radiology; 5% primary care; 6% other
Motley ¹²⁷ , UK, 1995	2 weeks in 1993	To determine the pattern of BCC treatment by dermatologists	166 consulting dermatologists in UK registered all BCC contacts in a 2-week period	Cross sectional	1,597 BCCs in 1,366 patients	Treatment pattern by UK dermatologists: 58% of tumors were treated with excision, 24% with curettage and cautery, 8% with radiotherapy, 8% with cryotherapy, 7% other treatments
Chen, US ³⁶ , 2006	1999- 2000	To estimate the cost of NMSC episode and the factors that impact those costs	Medicare Current Benificiary Survey	Cross sectional	372 NMSC patients with 497 tumors	Distribution of specialties providing treatment: 50% dermatologist; 6% surgeon; 7% primary care physician; 12% other; 26% multiple specialties Treatment setting: 64% physician's office; 2% inpatient; 29% outpatient; 2% surgical center; 3% other
Gudi ¹²⁸ , 2006	6 weeks in 2000	To assess the management of BCC in Scotland	42 consulting dermatologists in Scotland registered all BCCs for 6 weeks	Cross sectional	324 patients with 360 lesions	22% underwent diagnostic biopsy prior to definitive therapy. Treatment offered: 83% excision; 9% curettage and cautery; 4% cryotherapy; 2% radiotherapy; 2% other treatments
Streeton ¹³⁰ , AU, 2004	2004	To determine current treatments and the associated	205 general practitioners were asked to complete a questionnaire	Cross sectional	86 doctors reported information on 164 BCC	22% of the patients were referred to a specialist for treatment. Treatment by the GP: 87% excision; 6% cryotherapy; 3.3% curettage;

Table 3 Studies providing information on NMSC treatment patterns.

		healthcare costs of BCC treatment	for two BCC patients randomly identified from their records		patients with a total of 244 BCCs	0.8% Mohs' surgery;1.7% interferon; 1.2% other treatments
Stang ¹²⁶ , Germany, 2009	2005-2006	To provide quantitative information about the in- hospital management of skin cancer	Nationwide diagnosis related groups data from German hospitals	Cross sectional	98,484 hospitalizat ions with a primary diagnosis of NMSC	Approximately 58% of NMSC-related hospitalizations were at a dermatology dept; 22% at a surgery dept, including plastic surgery dept. Treatment distribution: 58% plastic surgery; 28% excision; 10% nonsurgical treatment; 1% radiotherapy; 2% chemotherapy; 7.5% skin biopsy.

Follow-up after treatment

The follow-up after NMSC diagnosis and treatment aims for the early detection of tumor recurrence and new lesions, as well as patient education, especially regarding sun protection^{90;91;119;120}. Due to the high incidence and relatively favorable prognosis, long-term follow-up is neither possible nor necessary to offer to all patients. The British and European guidelines do not recommend long-term follow-up to all patients, but acknowledge that it may be important for selected patients with poor prognostic factors, such as size >2 cm, tumors located in high risk areas, histological type, and immunosuppression^{90;91}.

The Danish Dermatological Society has published recommendations for the treatment and followup of NMSC patients in Denmark^{119;120}. The recommendations are that all patients should be offered follow-up within the first year and, in agreement with international guidelines, long-term follow-up should be offered individually^{119;120}.

Existing literature on follow-up after BCC treatment (Study IV)

We searched Medline to identify existing literature on follow-up after BCC treatment using the following Mesh term search and free text search:

- "Patient Participation"[Mesh] AND "Skin Neoplasms"[Mesh] OR ("Neoplasms, Basal Cell"[Mesh] OR "Neoplasms, Squamous Cell"[Mesh])
- follow-up practice AND non-melanoma skin cancer
- follow-up practice AND skin cancer
- attendance AND skin cancer
- patient participation AND skin cancer

We limited our search to population-based studies in humans that were published in English or Danish. In addition, the reference lists of selected publications were searched for other relevant articles.

Our search mainly resulted in studies of patients from skin cancer screening programs, especially melanoma skin cancer screening. The follow-up after BCC treatment also aims to screen for new skin cancers. However, the participants of a follow-up visit differ from the participants in screening programs because the main purpose of their visit is to assess the outcome of the treatment of one or more skin cancers.

Few studies exist on the clinical follow-up of BCC patients treated in routine dermatological practice. However, a Danish dermatology clinic published two studies reporting their follow-up of NMSC cases treated in their clinic, the majority of which were BCC^{124;125}. More than 80% of the patients with primary NMSCs were followed up to one year post-diagnosis, which decreased to just over 60% at 2 years^{124;125}. A UK-based study reported fewer patients, with 78% and just over 50% of patients attending 1 and 2-year follow-up visits, respectively¹³¹. Research has suggested that the follow-up of patients is associated with the choice of treatment and anatomic location of the NMSC¹³².

Economic burden of NMSC

The very high prevalence of BCC and SCC entails a significant challenge in terms of morbidity, public health management, and healthcare costs^{36;133}. Few economic evaluations have assessed the burden of NMSC treatments¹³⁴. Housmann *et al* estimated an annual mean Medicare payment of \$US562 million for NMSC from 1992 to 1995, and they found that NMSCs were among the five most costly cancers to Medicare¹³³. The cost of NMSC treatment depends greatly on the treatment modality, but it is also very dependent on whether treatment is conducted in a hospital or an office-based setting. Research on Medicare data has found that the mean cost of tumor management in an office-based setting was US\$500, whereas the costs in an ambulatory surgical center or hospital setting were US\$935 and US\$4,345, respectively³⁶. Another US study based on Medicare data estimated that the cost of tumor destruction was lowest on a per patient basis (US\$221), whereas the cost of radiotherapy was the highest (US\$1303)⁵⁰.

Conclusion

Already existing data sources can be used in the study of NMSC, keeping in mind the potential methodological problems of underreporting and incomplete registration of these cancers. However, new and accurate data on NMSC are needed for effective public health monitoring and intervention¹. Detailed data on NMSC and the treatment of NMSC in everyday clinical practice are important for surveillance, predicting prognosis, improving the quality of care and treatment, and for research purposes^{1;40;41}. Such data can be obtained from properly designed clinical databases and have the potential to become an attractive source of epidemiological research⁴⁰. The development of a clinical database that encompasses prognostic factors, treatment factors, and outcome is essential if an evidence-based health policy towards NMSC is to be developed¹. Data validation is crucial to assessing the usefulness of a clinical database as a valuable tool for answering clinical, administrative, and research questions¹³⁵.

Aims of this thesis

- a. To examine the association between hip fractures and NMSC using NMSC as a proxy for sun exposure (Study I).
- b. To develop the NMSC database, a database for registering NMSC, Bowen's disease, and keratoacanthomas in dermatology clinics, and to describe the content of the NMSC database, and to describe the treatment patterns in dermatology clinics in the Central and North Denmark Regions using this database (Study II).
- c. To examine the validity of the data in the NMSC database, including completeness of NMSC registration and the accuracy of key variables in the database (Study III).
- d. To examine factors that impact on attendance at follow-up visits after the treatment of basal cell carcinoma in dermatology clinics (Study IV).

Materials and Methods

Study design

Study I is a case-control study. The study cases were patients registered in the DCR with BCC or SCC. For each case, five population-based, age and gender-matched controls were selected using the Danish Civil Registration System. The exposure was a history of skin cancer prior to diagnosis of NMSC or the index date for the corresponding population control.

Study II is a descriptive study of the development, content, and potential use of the NMSC database and the treatment patterns in the affiliated clinics.

Study III is a validation study. We evaluated the completeness of the registration of patients and the accuracy of variables registered in the NMSC database. We conducted a cross-sectional study using patients in contact with the dermatology clinics providing information to the NMSC database between January 1 and June 30, 2008.

Study IV is a cohort study. We examined patient, tumors and treatment factors impact on attendance at follow-up visits after the initial treatment of NMSC.

Setting

Study I was conducted within the entire Danish population (5.3 million) using the DCR as the NMSC data source. **Studies II, III, and IV** were based on data from the NMSC database and conducted within the population-based health care system of the Central and North Denmark regions. The two regions have a combined population of 1.8 million (approximately 30% of the total Danish population) with a total of 19 dermatology clinics.

Data sources

The Danish Regional NMSC Dermatology Database

As a part of this PhD project, a regional clinical database for registering NMSCs in dermatology clinics was established. Data from the database was used in **Studies II, III, and IV**.

Development of the NMSC database

The NMSC database was initiated in 2007 in cooperation with the Danish Dermatological Society and Danish Dermatologists' Organization. The NMSC database steering committee includes

dermatologists from both hospital and office-based clinics, and representatives from a center monitoring the quality of treatment in the Danish health care system. The steering committee determined the data to be collected in the database and selected key indicators with which to monitor the quality of the diagnosis and treatment of NMSC in dermatology clinics (Appendix 1 and 2). A common interface form ensures standardized data collection.

An online registration system was developed and tested in two dermatology clinics in 2007. The online registration system opened for registration to all dermatology clinics in the region on January 1, 2008. In April 2009, the Danish National Board of Health approved the database as a regional clinical database. Since that time, database registration has been mandatory for dermatologists in private clinics in the Central Denmark region and for certain clinics in the North Denmark region. In August 2010, the database was granted permission to operate as a national clinical database.

Content of the NMSC database

The NMSC database contains detailed information on the type of NMSC, treatment-related factors, and prognosis-related factors after treatment in the dermatology clinics⁴². On the day of treatment, the treating dermatologist completes a questionnaire with detailed information on prognostic and treatment- related variables: clinical and histological diagnosis, localization, size, previous skin cancer history, skin type, evidence of metastases, and treatment (Appendix 1)⁴². In the database, BCC patients are scheduled for two follow-up visits, one at 3 months (between 0 and 6 months) and one at 12 months (between 6 and 15 months) after treatment. At these visits, information on recurrence, the cosmetic result, and complications are registered (Appendix 2)⁴².

The Danish Civil Registration System (CRS)

All studies used data from the CRS, which contains information on all Danish citizens, who are assigned a unique 10-digit civil personal registration number (CPR number) at birth or immigration. Information on changes in vital status, such as emigration and death, are registered in the CRS. The unique CPR number allows a link between the Danish medical and population-based databases (Figure 2).¹³⁶

Figure 2 Linkage of the Danish medical databases used in this thesis



The Danish National Pathology Registry (DPR)

We used data from the DPR in **Study III**³⁴. The registry is described in the section; Danish NMSC data sources (page 5).

Danish National Patient Registry (DNPR)

Studies I and IV used data from the DNPR³⁵. The registry is described in the section; Danish NMSC data sources (page 6).

The Danish Cancer Registry

Study I used data from the DCR³¹. The registry is described in the section; Danish NMSC data sources (page 5).

The Integrated Database for Labor Market Research (IDA)

The IDA database was used in **Study I**. This database was established in 1980 and is administered by Statistics Denmark¹³⁷. The IDA contains more than 250 variables characterizing the Danish population and the population's attachment to the labor market. All Danish citizens are characterized by data on their family and household, education, employment, and income. The data are supplied by tax authorities, educational institutions, and employment services. The IDA database is updated annually.

Medical record review

In **Study III**, we used data from the medical records of two dermatology clinics affiliated with the NMSC database. For each patient diagnosed on the given day with BCC, SCC, Bowen's disease, or keratoacanthoma, information on the following variables was identified in the medical record: anatomical location of the tumor, treatment date, treatment modality, previous skin cancer history (first cancer or history of previous skin cancer(s)), and tumor history (new tumor or recurrence of previously treated tumor). Likewise, recurrence and complications identified at a follow-up visit were registered for patients who later attended a follow-up visit.

Data were entered into EpiData 3.1, blinded from the registration in the NMSC database. Subsequently, the data was compared with the data in the NMSC database. Where information registered in the NMSC database disagreed with the information in the medical record, the medical records were reviewed again and any uncertainty discussed and clarified with an independent dermatologist.

Definition of study population and variables

Definition of study population in Studies I, II and IV

In **Study I**, we used the DCR to identify all patients with a diagnosis of BCC or SCC recorded between January 1, 1990 and December 31, 2005 (SNOMED codes: BCC: 80903, 80913, 80923, 80933, 80943, 80953; SCC: 80513, 80523, 80703, 80713, 80743, 80753, 80763). For each case, five population-based, age and gender-matched controls were selected in the CRS using risk-set sampling.

In **Study II**, we identified NMSC, Bowen's disease and keratoacanthoma patients registered in the NMSC database between January 1, 2008 and July 14, 2010.
In **Study IV**, we identified all BCC patients registered in the NMSC database. We included patients diagnosed either clinically or histologically. Any histologically verified diagnosis overruled a clinical diagnosis. We excluded all patients with tumors who were referred elsewhere for treatment (e.g., department of dermatology, plastic surgery, or oncology), as these patients were followed at the hospital and would, therefore, be omitted from the database. We also excluded patients who died during follow-up. We examined the attendance of follow-up visits registered in the NMSC database for two time intervals: 0-6 months and 0-15 months following treatment. In order to obtain an equal follow-up time for attendees and non-attendees at follow-up, we constructed two study populations. The first study population consisted of patients with at least 6 months of follow-up.

Definition of study population, gold standard, and outcome in Study III

Table 4 provides an overview of the design of Study III described below.

Completeness of patients with tumors verified histologically: To calculate the completeness of the registration of patients diagnosed histologically with BCC, SCC, Bowen's disease, and keratoacanthoma in the NMSC database, all histologically verified BCC, SCC, Bowen's disease, and keratoacanthoma cases registered in the NMSC database from January 1 to June 30, 2008 were used as study population. As a gold standard, we used the registrations of patients with BCC, SCC, Bowen's disease, or keratoacanthoma in the Danish National Pathology Registry during the same time-period (please see article III for detailed SNOMED codes).

Completeness of all NMSC patients: The completeness of all tumors registered in the NMSC database, including tumors only clinically diagnosed, was assessed by reviewing medical records in the two clinics. Three working days per month for a period of six months were randomly selected for each clinic (a total of 36 working days). All contacts to the clinics on those days were reviewed via medical records in order to cover all contacts with patients diagnosed with NMSC, Bowen's disease, or keratoacanthoma.

Accuracy: The patients identified in both the NMSC database and the medical record review were used to assess the accuracy. The medical records were used as a gold standard to assess the accuracy of the following registered variables: anatomical location of the tumor, treatment date, treatment modality, previous skin cancer history (first cancer ever yes/no), tumor history (new

tumor or recurrence of previously treated tumor), and recurrence and complications at follow-up. The DPR was used to assess the accuracy of the histological diagnoses registered in the database. *Completeness of follow-up:* The completeness of the registration of follow-up visits in the database was assessed using the same cohort of patients registered in both the NMSC database and the medical record review. However, we excluded patients referred to the hospital for treatment and patients with Bowen's disease and keratoacanthoma lesions because it is not mandatory for dermatologists to register follow-up visits for these patients.

Table 4 Design of Study III.

Period	Study population	Gold standard	Outcome(s)
January 1 -	All patients with	The Danish	Completeness of patients
June 30, 2008	histologically verified tumors	National	with tumors verified
	in the NMSC database	Pathology	histologically
		Registry	
3 working days	All patients with tumors in	Medical record	Completeness of all
per month for	the NMSC database	review	NMSC patients
6 months			
3 working days	All patients with tumors in	Medical record	PPV, NPV, SE, and SP
per month for	the NMSC database	review,	of key variables
6 months		The Danish	
		National	
		Pathology	
		Registry	
3 working days	All patients with BCC or	Medical record	Completeness of follow-
per month for	SCC tumors in the NMSC	review	up visits
6 months	database (excluding patients		
	with tumors referred to		
	treatment at the hospital)		

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; SE, sensitivity; SP, specificity.

Definition of exposures, outcomes, and confounding factors in Studies I, II and IV

Table 5 provides an overview of the design of Studies I, II and IV

Study	Period	Study population	Exposure	Outcome(s)
Study I	1990-2005	BCC and SCC	A history of hip	BCC and SCC
-		patients registered in	fracture	
		the DCR and		
		population controls		
		from the CRS		
Study II	January 1, 2008	NMSC, Bowens	Gender, age, history	
	and July 14, 2010	disease and	of skin cancer, tumor	
		keratoacanthoma	history, size, location	
		registered in the	of tumor, treatment	
		NMSC database	modality	
Study IV	January 1, 2008-	BCC patients	Gender, age, history	Attendance at
	April 1, 2009 ¹	registered in the	of skin cancer, tumor	follow-up after
		NMSC database	history, size, location	treatment of
	January 1, 2008-	1	of tumor, treatment	BCC
	February 1, 2010^2		modality, Charlson's	
	5,		Index, and clinic	

Table 5 Design of Studies I, II and IV.

¹Patients with 6 months of follow-up after initial treatment. ²Patients with 15 months of follow-up after initial treatment.

Exposure

In **Study I**, data on hip fractures prior to the diagnosis of skin cancer or the corresponding index date were obtained from the DNPR (ICD-8 codes 820.00 and 820.01, ICD-10 codes S72.0 and S72.1).

In **Study II**, we retrieved information on gender, age, previous skin cancer history (first cancer or history of previous skin cancer(s)), tumor history (new tumor or recurrence of previously treated tumor), size, anatomical location of the tumor(s), and treatment modality from the NMSC database.

In **Study IV**, we examined patient-, tumors and treatment-factors associated with attendance at follow-up after the treatment of BCC. We retrieved information on gender, age, skin cancer history, tumor history (new tumor or recurrence of previously treated tumor), tumor size, tumor location, and treatment modality from the NMSC database. We used the Charlson Comorbidity Index (CCI)

to estimate comorbidity levels among patients in **Study IV**^{138;139}. Using the DNPR, we identified all post-1977 diagnoses of the study patients and used them to compute a CCI score for each patient. The patients were categorized as having coexistent diseases if CCI>0.

Outcome

The outcome in **Study I** was a registration of BCC and/or SCC in the DCR between January 1, 1990 and December 31, 2005. If the patients were registered with both SCC and BCC, the patient was categorized as SCC. Cases were stratified according to the anatomical site of the NMSC: head and neck (ICD-10 C44.0-C44.4), trunk and extremities (ICD-10: C44.5-C44.7), and tumors at multiple sites (ICD-10 C44.8).

In **Study IV**, outcome was considered as attendance at early follow-up, as well as attendance overall within the first 15 months. Early follow-up was defined as at least one follow-up visit registered in the NMSC database 0-6 months following treatment. Overall, follow-up was defined as at least one follow-up visit within 0-15 months following treatment.

Confounding factors

Study I: A number of chronic diseases may influence the association between a history of hip fracture and NMSC. We obtained data from the DNPR on any prior hospital diagnoses of nondiabetic endocrine disorder, diabetes, gastrointestinal disorders, leukemia and lymphoma, connective tissue disease, alcohol abuse, chronic obstructive pulmonary disease, neurological disorders leading to an increased risk of falls, dementia, congestive heart failure, cerebrovascular disease, solid cancer, malignant melanoma, and chronic renal disease since 1977^{80;140} (please see article I for detailed ICD codes). Both inpatient and outpatient diagnoses were included. Occupational level, education, income, and marital status may also be associated with both hip fracture and NMSC, and information on these variables was retrieved from the IDA database.

Study IV: The patient-, tumors and treatment-factors described above were also treated as confounding factors. In addition, we retrieved information on the treating clinic from the NMSC database.

Statistical analyses

In **Study I**, we constructed contingency tables for BCC and SCC cases and controls based on demographic characteristics (age and gender), the anatomic site of the tumor, prior hospitalizations

for existing chronic diseases, and SES. We used conditional logistic regression to compute ORs and 95% confidence intervals (CIs) for the relationship between a history of hip fracture and BCC and SCC, respectively, while adjusting for chronic diseases and SES. We conducted analyses both with and without information on education, and found that this variable did not change our estimates. Thus, we excluded education in the final analyses. We used conditional logistic regression to compute ORs according to tumor location (i.e., head and neck, trunk/extremities, and multiple sites).

Because we used risk-set sampling in this case-control study, the estimated exposure OR is an unbiased estimate of the incidence ratio¹⁴¹. We repeated the analyses with age and gender stratification in order to assess the effect of these variables.

In **Study II**, patient, tumor, and treatment-related characteristics registered in the NMSC database were described with frequency tables.

In Study III, completeness was calculated as a proportion.

Completeness of histologically verified tumors=

The number of patients diagnosed with a tumor and registered in the NMSC database and the Danish National Pathology Registry The number of patients with the same diagnosis registered in the Danish National Pathology Registry

Completeness of registration of all tumors, including clinically diagnosed tumors=

The number of patients with a clinically diagnosed tumor registered in the NMSC database and in the medical record The number of patients recorded in the medical record with either type of diagnosis

Completeness of registration of 1st follow-up visits=

The number of patients registered with at least one follow-up visit in the database between 0-6 months after initial treatment The number of patients registered with a follow-up visit in the medical records (0-6 months)

The completeness of registration of 2nd follow-up visits=

The number of patients registered with at least one follow-up visit in the database between _____6-15 months after initial treatment _____

The number of patients registered with a follow-up visit in the medical records (6-15 months)

The accuracy of key variables in the NMSC database outlined above was assessed by calculating the positive predictive value (PPV), negative predictive value (NPV), sensitivity (SE), and specificity (SP) (Table 6).

Table 6 Formulas to calculate the positive predictive value (PPV), negative predictive value (NPV), sensitivity (SE), and specificity (SP).

			Medical re-			
		NMSC database	Yes	No		
e.g., F	irst skin cancer ever	Yes No	a c	b d	PPV=a/(a+b) NPV=c/(c+d)	
			SE=a/(a+c)	SP=b/(b+d)		
PPV The proportion of patients registered with 'yes' for a given variable <i>in the database</i> confirmed in <i>the medical record</i> (i.e. the variable; diagnosis according to the DPR) For variables: 'diagnosis overall', 'treatment overall', 'size', localization', and 'treatment date' PPVs were the proportion of a given variable registered in <i>the database</i> confirmed in the <i>medical record/DPR</i>						
NPV The proportion of patients registered with 'no' for a given variable <i>in the database</i> confirmed in <i>the medical record</i> (i.e. the variable; diagnosis according to the DPR)						
SE	SE The proportion of patients registered with 'yes' for a given variable <i>in the medical record</i> , who were registered with a 'yes' in <i>the database</i> (i.e. the variable diagnosis, according to the DPR)					
SP	The proportion of patients with 'no' for a given variable <i>in the medical record</i> , who were registered with a 'no' in <i>the database</i> (i.e. the variable diagnosis, according to the DPR)					

In **Study IV**, we examined registrations of attendance at early follow-up following treatment (at least one follow-up visit within the first 6 months), and late follow-up (at least one follow-up visit between 6 to 15 months following treatment), as well as the overall follow-up within the first 15 months (at least one follow-up visit within the first 15 months). In Study III, we examined the completeness of registration of follow-up visits⁴² and found a completeness of registration 85% and 69%, for the early and late follow-up visits, respectively⁴². Accounting for the estimated incompleteness of registration of follow-up visits, we estimated attendance at early and late follow-up visits of patient and clinical factors by attendance at follow-up visits 0-6 months (early follow-up) and 0-15 months after initial treatment (overall follow-up).

We assumed the incomplete registration of follow-up visits to be non-differential with respect to the patient/tumor/treatment factors and attendance, and each candidate factor was entered into a logistic regression model to calculate the odds ratio (OR) and associated 95% confidence interval (95%CI) estimates for attendance at follow-up. Adjusted ORs were calculated in a multiple logistic

regression model including the patient, clinical, and treatment factors and data on the treating clinic. Because clinics 4-10 were the latest to join the database and therefore had the least experience registering in the database, we re-analyzed the data excluding clinics 4-10. Finally, we re-analyzed the data excluding patients registered with more than one tumour.

Main results

Study I

Descriptive data

Using the DCR, we identified 69,506 BCC patients and 11,526 SCC patients over the age of 40 years who were recorded in the registry between January 1, 1990 and December 31, 2005.

History of hip fracture and risk of BCC

The overall number of patients with a history of hip fracture was 1,930 (2.8%) among BCC patients and 10,914 (3.1%) among controls, corresponding to an adjusted OR of 0.90 (95% CI: 0.85-0.94) for BCC among patients with a history of hip fracture. After stratification for the location of the BCC tumor, the number of patients with a history of hip fracture was 1,158 (3.5%) among BCC patients with head and neck tumors and 6,044 (3.6%) among their controls, corresponding to an adjusted OR of 0.96 (95% CI: 0.89-1.02). Among patients with tumors on the trunk or extremities and their corresponding controls, 334 (2.2%) and 2,019 (2.6%), respectively, had a history of hip fracture, corresponding to an adjusted OR of 0.85 (95% CI: 0.75-0.96). Among patients with tumors at multiple sites and their controls, 404 (2.0%) and 2,684 (2.7%), respectively, had a history of hip fracture, corresponding to an adjusted OR of 0.77 (95% CI: 0.69-0.86; Table 7). Risk estimates stratified by gender and age were virtually the same in all strata.

History of hip fracture and risk of SCC

The prevalence of previous hospitalization for hip fracture was 657 (5.7%) among SCC patients and 3,047 (5.3%) in the control group (Table 8). The corresponding adjusted OR for SCC among patients with a history of hip fracture was 1.07 (95% CI: 0.98-1.17). After stratification for the anatomic location of the SCC, the number of patients with a history of hip fracture was 422 (6.4%) among BCC patients with head and neck tumors and 1,874 (5.7%) among their controls, corresponding to an adjusted OR of 1.14 (95% CI: 1.02-1.28). Among patients with tumors on the trunk or extremities and their controls, 142 (5.1%) and 652 (4.7%), respectively, had a history of hip fracture, corresponding to an adjusted OR of 1.10 (95% CI: 0.91-1.33). Among patients with

tumors at multiple sites and their controls, 81 (4.1%) and 440 (4.5%), respectively, had a history of hip fracture, corresponding to an OR of 0.91 (95% CI: 0.71-1.17; Table 8). Risk estimates stratified by gender and age were virtually the same.

	Previous hip fractur their co	e among cases and ontrols	ORs for BCC		
	Cases n (%)	Controls n (%)	Crude OR (95% CI)	Adjusted OR ¹ (95% CI)	
Total	1,930 (2.8)	10,914 (3.1)	0.87 (0.83-0.92)	0.90 (0.85-0.94)	
Stratified by localization					
Head and neck	1,158 (3.5)	6,044 (3.6)	0.95 (0.89-1.02)	0.96 (0.90-1.02)	
Trunk/extremities	334 (2.2)	2,019 (2.6)	0.81 (0.72-0.92)	0.85 (0.75-0.96)	
Multiple sites	404 (2)	2,684 (3)	0.74 (0.66-0.82)	0.77 (0.69-0.86)	
Unknown localization	34 (4)	167 (4)	1.02 (0.69-1.51)	1.07 (0.72-1.60)	
Stratified by age (years)					
≤65	107 (-)	594 (-)	0.90 (0.73-1.10)	0.97 (0.79-1.09)	
66-80	648 (2)	3,777 (3)	0.85 (0.78-0.93)	0.88 (0.80-0.95)	
$80+^{2}$	1,175 (10)	6,543 (11)	0.88 (0.83-0.94)	0.90 (0.84-0.97)	
Stratified by gender					
Male	476 (2)	2,846 (2)	0.83 (0.75-0.92)	0.87 (0.79-0.96)	
Female	1,454 (4)	8,068 (4)	0.89 (0.84-0.94)	0.91 (0.86-0.97)	

Table 7 Odds ratios (ORs) for BCC among cases with a history of hip fracture.

¹Adjusted for occupational level, income, marital status, non-diabetes endocrine diseases, diabetes, gastrointestinal disorders, leukemia and lymphoma, connective tissue diseases, alcohol abuse, chronic pulmonary disease, neurological disease, dementia, congestive heart disease, solid cancer (except skin cancer), malignant melanomas, cancer, and chronic renal diseases.²Occupational level was excluded in the adjusted analyses of the 80+ stratum. Abbreviations: n, numbers; CI, confidence interval

	Previous hip fractur cont	re among cases and rols	ORs for SCC		
	Cases	Controls	Crude OR	Adjusted OR ¹	
	n (%)	n (%)	(95% CI)	(95% CI)	
Total	657 (6)	3,047 (5)	1.09 (1.00-1.20)	1.07 (0.98-1.17)	
Stratified by localization					
Head and neck	422 (6)	1,874 (6)	1.14 (1.02-1.28)	1.11 (0.99-1.24)	
Trunk/extremities	142 (5)	652 (5)	1.10 (0.91-1.33)	1.09 (0.90-1.33)	
Multiple sites	81 (4)	440 (5)	0.91 (0.71-1.17)	0.94 (0.73-1.21)	
Unknown localization	12 (6)	68 (6)	0.87 (0.45-1.67)	0.82 (0.42-1.61)	
Stratified by age (years)					
<65	10 (-)	39 (-)	1.28 (0.64-2.58)	1.05 (0.50-2.20)	
65-80	126 (3)	662 (3)	0.95 (0.78-1.16)	0.92 (0.75-1.12)	
$> 80^{2}$	521 (11)	2,346 (10)	1.13 (1.02-1.26)	1.14 (1.03-1.27)	
Stratified by gender					
Male	222 (3)	1,048 (3)	1.07 (0.92-1.24)	1.03 (0.89-1.20)	
Female	435 (10)	1,999 (9)	1.11 (0.99-1.24)	1.09 (0.98-1.23)	

Table 8 Odds ratios (ORs) for SCC among cases with a history of hip fracture.

¹Adjusted for occupational level, income, marital status, non-diabetes endocrine diseases, diabetes, gastrointestinal disorders, leukemia and lymphoma, connective tissue diseases, alcohol abuse, chronic pulmonary disease, neurological disease, dementia, congestive heart disease, solid cancer (except skin cancer), malignant melanomas, cancer, and chronic renal diseases.

²Occupational level was excluded in the adjusted analyses of the 80+ stratum. Abbreviations: n, numbers; CI, confidence interval

Study II

Between January 1, 2008 and July 14, 2010 a total of 5,433 tumors were registered in the NMSC database for a total of 3,782 persons. The NMSC database provides detailed clinical data on the registered tumors.

Patient and tumor characteristics

Approximately 90% of all registered tumors were BCCs. SCC and Bowen's disease each accounted for approximately 4% of all tumors, and keratoacanthoma approximately 2%. Fifty-eight percent of the BCC tumors were clinically diagnosed as nodular BCC, 39% as superficial BCC, 1% morphea BCC, and 2% unknown. Patients with BCC had the lowest median age (68 years), whereas SCC patients had the highest median age (79 years). One-third of the patients had a previous skin cancer at the time of first registration in the database, and 23% of the patients were registered in the database with more than one tumor. Approximately 9% of BCC and 5% of SCC tumors registered in the database were recurrent tumors. The head and neck area was the anatomical site of almost half of all BCC, while 73% of all SCC tumours were located in this area. The trunk accounted for about 34% of all BCC, but only 8 % of the SCC. Little difference was found in the median size of the individual tumor types: 9 mm for BCC, 10 mm for SCC and Bowen's disease, and 12 mm for keratoacanthoma.

Tumor treatment

Curettage with or without cautery was the most commonly used treatment independent of anatomical site, and was used in 78% of BCC tumors, 52% of SCC tumors, 83% of Bowen's disease, and 78% of keratoacanthomas. Nine percent of the BCC tumors, 5% of Bowen's disease, and 34% of SCC tumors were referred to hospital departments for treatment, primarily to plastic surgery and radiotherapy. A total of 3% of the BCCs and 4% of Bowen's disease were treated non-surgically (i.e., imiquimod or photodynamic therapy in the dermatology clinics; Table 9). BCC tumors on the nose, ears, lips, and eye area were less likely to be treated with curettage (72%) compared to tumors on the body (83%), and they were more likely to be referred to the hospital for treatment (21%) compared to tumors on the body (3%). Almost half (n=23) of the SCC tumors on the nose, ears, lips, and eye area were treated with curettage, with or without cautery (lips: 23%, n=3; eyes: 100%, n=1; ears: 45%, n=9; nose: 67%, n=10).

	Curettage ± cautery (%)	Excision (%)	Non-surgical treatment (%)	Referral to hospital (%)	Other treatment (%)
Total number of tumors	4,285	321	172	527	128
Anatomical site					
BCC overall	3,883	281	163	429	111
Nose, ears, lips, and eye area	551 (72)	28 (4)	13 (2)	158 (21)	11 (2)
Other sites on the head and neck	1,366 (78)	102 (6)	46 (3)	208 (12)	28 (2)
Body	1,945 (83)	150 (6)	103 (4)	62 (3)	72 (3)
Unknown	21 (88)	1 (4)	1 (4)	1 (4)	0 (0)
SCC	128	22	1	82	7
Nose, ears, lips, and eye area	23 (47)	3 (6)	1 (2)	19 (39)	3 (6)
Other sites on the head and neck	69 (55)	6 (5)	0 (0)	47 (38)	3 (2)
Body	30 (51)	12 (20)	0 (0)	16 (27)	1 (2)
Unknown	6 (86)	1 (14)	0 (0)	0 (0)	0 (0)
Bowen's disease	183	6	8	9	9
Nose, ears, lips, and eye area	28 (90)	0 (0)	0 (0)	1 (3)	2 (6)
Other sites on the head and neck	83 (89)	1(1)	3 (3)	3 (3)	3 (3)
Body	65 (77)	5 (6)	5 (6)	5 (6)	4 (5)
Unknown	7 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Keratoacanthoma	91	12	0	7	1
Nose, ears, lips, and eye area	19 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Other sites on the head and neck	28 (74)	4 (11)	0 (0)	6 (16)	0 (0)
Body	42 (82)	7 (14)	0 (0)	1 (2)	1 (2)
Unknown	2 (67)	1 (33)	0 (0)	0 (0)	0 (0)

Table 9 Treatment in relation to anatomical site.

Study III

A total of 288 patients were registered in the NMSC database between January 1 and June 30, 2009.

Completeness. The overall completeness of patient registration in the database was 62% when the DPR was used as a gold standard (Table 10) but differed by clinic. The completeness in clinic 1 was 93%, whereas the completeness in clinic 2 was 40%. Based on the medical record review, the completeness of patient registration in the database was 76% overall: 95% and 60% in clinics 1 and 2, respectively (Table 10).

The completeness of the registration of 1st follow-up visits in the NMSC database compared to registration in the medical record review was 85% but varied by: 100% and 71% in clinics 1 and 2, respectively (Table 11). The completeness of the registration of 2nd follow-up visits was 69% overall: 74% and 63% in clinics 1 and 2, respectively (Table 11).

	Patients registered in the NMSC database (n)	Patients registered in the DPR (n)	Degree of completeness (Evaluation:DP R) % (95% CI)	Patients registered in the NMSC database (n)	Patients with NMSC according to medical record review (n)	Degree of completeness (Evaluation: medical records) % (95% CI)
Overall patients	288	452	62 (58-67)	67	88	76 (66-85)
Completeness for each clinic						
Patients clinic 1	178	182	93 (88-94)	39	41	95 (84-99)
Patients clinic 2	110	270	40 (34-46)	28	47	60 (44-74)

 Table 10 Completeness of the registration of patients in the NMSC database.

Abbreviations: n, numbers; CI, confidence interval

Table 11 Completeness of the registration of follow-up visits in the NMSC database.

	1 st Follow-up visit (<6 months after treatment)					Follow-up visit (6	-15 months afte	er treatment)
	Total number of patients registered in the NMSC database	Follow-up visits registered in the NMSC database (n)	Follow-up visits registered in medical records (n)	Degree of completeness of 1 st follow-up visits % (95% CI)	Patients registered in the database (n)	Follow-up visits registered in the database (n)	Follow-up visits registered in medical records (n)	Degree of completeness of 2 st follow-up visits % (95% CI)
Overall	54	39	46	85 (71-94)	54	24	36	67 (49-81)
Clinic 1	29	22	22	100 (85-100)	29	14	19	74 (49-91)
Clinic 2	25	17	24	71 (49-87)	25	10	17	59 (33-82)

Abbreviations: n, numbers; CI, confidence interval

Accuracy of the registered variables. The PPV, NPV, SE, and SP of histologically verified diagnoses were 100% when using the DPR as a gold standard (Table 12). The PPV, NPV, SE, and SP of the other variables using the medical record review as a gold standard varied between 67% and 100%. For detailed information, please see article III. PPV, NPV, SE and SP of recurrences registered at either 1st or 2nd follow-up were 100%, 98%, 75%, and 100%, however the number of recurrences was low and the medical record review revealed an incomplete registration of recurrences mainly due to the incomplete registration of follow-up visits. At 1st follow-up visits, two recurrences were registered in the NMSC database. The medical record review revealed one additional recurrence which had been mistakenly registered as no recurrence. At 2nd follow-up visit, one recurrence was registered. The medical record review revealed four additional recurrences which had not been registered due to incomplete registration of follow-up visits, and the sensitivity

of registration of recurrence, including the missing registration of follow-up visits, was then 38% (3/8).

		D confi	PR irmed	0				
	NMSC database	Yes (n)	No (n)	Total (n)	PPV % (95% CI)	NPV % (95% CI)	SE % (95% CI)	SP % (95% CI)
Histological diagnosis overall	Total	78	0	78	78/78= 100(95-100)			
Basal cell carcinoma	Yes (n) No(n)	72 6	0 0	72 6	72/72= 100(95 -100)	6/6= 100(54-100)	72/72= 100(95-100)	6/6= 100(54-100)
Squamous cell carcinoma	Yes (n) No(n)	2 76	0 0	2 76	2/2= 100(16-100)	76/76= 100(95-100)	2/2= 100(16-100)	76/76= 100(95-100)
Mb. Bowen	Yes (n) No(n)	2 76	0 0	2 76	2/2= 100(16-100)	76/76= 100(95-100)	2/2= 100(16-100)	76/76= 100(95-100)
Keratoacan- thoma	Yes (n) No (n)	2 76	0 0	2 76	2/2= 100(16-100)	76/76= 100(95-100)	2/2= 100(16-100)	76/76= 100(95-100)

Table 12 Positive predictive value (PPV), negative predictive value (NPV), sensitivity (SE), and specificity (SP) of the histological diagnosis registered in the NMSC database as verified with DPR

Abbreviations: n, numbers; CI, confidence interval

Study IV

A total 2,348 patients were registered in the NMSC database with a BCC and had at least 6 months of follow-up after the first registered treatment. Of the 2,348 patients, 1,759 were registered with one tumour only. A total of 1,116 patients had at least 15 months of follow-up, of whom 787 were registered with only one tumour.

In all, 82% of all patients were registered with at least one follow-up visit within the total follow-up period of 15 months. A total of 69% were registered with an early follow-up between 0 and 6 months after treatment, and 50% were registered with a late follow-up 6-15 months after treatment. Accounting for the known incompleteness of registration of follow-up visits, 81% and 72% of patients attended early and late follow-up, respectively

Factors associated with higher likelihood of attendance at follow-up

Patients with tumors located in "high risk" areas – nose, ears, lips, or eye area - were more likely to attend follow-up visits than patients with tumors on the trunk and extremities (adjusted OR 1.42, 95% CI 1.07-1.91 for early follow-up; adjusted OR 1.96, 95% CI 1.11-3.46 for overall follow-up), and more likely to attend than patients with tumours on other parts of the head and neck (adjusted

OR 1.24, 95% CI 0.94-1.65 for early follow-up; adjusted OR 2.00, 95% CI 1.15-3.48 for overall follow-up). In contrast, we found little difference in the likelihood of attendance among patients with tumors located in the head and neck region outside the "high risk" areas compared to patients with tumors located on the trunk and extremities (adjusted OR 1.15, 95% CI 0.92-1.43 for early follow-up; adjusted OR 0.98, 95% CI 0.67-1.42 for over all follow-up). Tumor size impacted attendance at follow-up; patients with at least one tumor larger than 5 mm were more likely to attend follow-up visits than patients with tumors smaller than 5 mm (Table 13). However, the risk estimates were imprecise.

The majority of tumors were treated with curettage, with or without cautery, causing imprecise estimates for the other treatments. Patients who received curettage (reference group) were most likely to attend follow-up visits, with the exception of patients who received more than one type of treatment, who were more likely to attend early follow-up but less likely to attend overall follow-up (Table 13).

Factors associated with lower likelihood of attendance at follow-up

An age over 85 years was associated with lower attendance in both early follow-up (adjusted OR 0.58, 95% CI 0.40-0.84) and overall follow-up (adjusted OR 0.64, 95% CI 0.33-1.23) compared to an age younger than 65 years. Having a coexisting disease was associated with a lower likelihood of attendance at follow-up (crude ORs 0.72, 95%CI: 0.60-0.86 and 0.73, 95%CI: 0.54-0.99 for early and overall follow-up). After adjustment there was still a trend towards lower attendance (adjusted OR 0.89, 95% CI 0.69-1.14 for early follow-up; adjusted OR 0.81, 95% CI 0.56-1.17 for overall follow-up). Similarly, a previous skin cancer diagnosis was associated with lower attendance at follow-up; the adjusted ORs for attendance at early follow-up in patients with 1-5 and >5 previous tumors were 0.75 (95% CI: 0.60-0.93) and 0.57 (95% CI: 0.40-0.81), respectively, and 0.71 (95% CI: 0.47-1.06) and 0.55 (95% CI: 0.31-0.98), respectively, for overall attendance at follow-up.

and patient, tailor and treatment related factors.								
	Attendance at fol	low-up within 0-6	Attendance at follow-up within 0-15					
	months after in	nitial treatment	months after i	nitial treatment				
	Crude OR ⁴	Adjusted OR ³	Crude OR ⁴	Adjusted OR ⁵				
	(95% CI)	(95% CI)	(95% CI)	(95% CI)				
Gender								
Male (ref)	1	1	1	1				
Female	1.10 (0.92-1.31)	1.07 (0.89-1.31)	1.08 (0.80-1.47)	1.06 (0.75-1.50)				
Age								
Age <65 (ref)	1	1	1	1				
Age ≥ 65 and < 75	0.93 (0.75-1.16)	0.90 (0.71-1.15)	0.98 (0.67-1.42)	0.96 (0.62-1.48)				
Age \geq 75 and $<$ 85	0.86 (0.68-1.08)	0.83 (0.63-1.08)	0.92 (0.61-1.37)	0.91 (0.57-1.47)				
Age≥85	0.65 (0.47-0.89)	0.58 (0.40-0.84)	0.60(0.35-1.04)	0.64 (0.33-1.23)				
Number of previous skin cancers ¹								
0 (ref)	1	1	1	1				
1-5	0.72 (0.59-0.87)	0.75 (0.60-0.93)	0.57 (0.41-0.80)	0.71 (0.47-1.06)				
>5	0.50 (0.37-0.68)	0.57 (0.40-0.81)	0.46 (0.27-0.76)	0.55 (0.31-0.98)				
Patient registered with a recurrent	tumor							
No (ref)	1	1	1	1				
Yes	1.14 (0.85-1.53)	1.13 (0.80-1.60)	0.90 (0.57-1.43)	1.06 (0.61-1.82)				
Patient's largest registered tumor								
<5 mm (ref)	1	1	1	1				
≥5 mm & <10mm	1.30 (0.95-1.77)	1.29 (0.91-1.82)	1.13 (0.72-1.78)	1.19 (0.71-1.99)				
≥10 mm & <20 mm	1.49 (1.09-2.04)	1.33 (0.93-1.89)	1.49 (0.92-2.41)	1.30 (0.76-2.25)				
≥20 mm	1.30 (0.90-1.88)	1.41 (0.92-2.14)	1.64 (0.79-3.38)	1.98 (0.83-4.57)				
Tumor location	•		•					
Trunk and extremities (ref)	1	1	1	1				
Head and neck - low risk area	1.12 (0.92-1.36)	1.15 (0.92-1.43)	1.02 (0.73-1.41)	0.98 (0.67-1.42)				
Head and neck - high risk area ²	1.40 (1.09-1.80)	1.42 (1.07-1.91)	2.00(1.23-3.25)	1.96 (1.11-3.46)				
Subanalysis of head and neck tumo	rs according to risk	area ²						
Head and neck - low risk area		1						
(ref)	1		1	1				
Head and neck - high risk area	1.24 (0.96-1.61)	1.24 (0.94-1.65)	1.97(1.20-3.23)	2.00 (1.15-3.48)				
Coexisting disease ¹								
No (ref)	1	1	1	1				
Yes	0.72 (0.60-0.86)	0.89 (0.69-1.14)	0.73 (0.54-0.99)	0.81 (0.56-1.17)				
Treatment modality								
Curettage ± cautery (ref)	1	1	1	1				
Excision	0.81 (0.59-1.13)	0.93 (0.58-1.30)	0.62 (0.37-1.04)	0.57 (0.32-1.01)				
Nonsurgical treatments	0.83 (0.51-1.35)	0.90 (0.50-1.62)	0.65 (0.30-1.40)	0.53 (0.22-1.26)				
Other treatments ³	0.43 (0.19-1.00)	0.52 (0.17-1.55)	0.20 (0.06-0.63)	0.41 (0.11-1.53)				
More than one treatment	1.45 (0.74-2.87)	1.90 (0.79-4.59)	0.48 (0.17-1.40)	0.78 (0.21-3.07)				
Treatment variable missing	not included	not included	not included	not included				

Table 13 Odds ratio (OR) estimates for the association between attendance at follow-up and patient, tumor and treatment-related factors.

¹First time entering the database, ²"High risk" area: tumor located around eyes, nose, lips, or ears, ³Cryotherapy or tangential excision with or without other treatments, ⁴Logistic regression, ⁵Adjusted for gender, age, number of previous skin cancers, recurrent tumor, tumor size, tumor location, coexisting disease, and treatment modality. Abbreviations: CI, confidence interval

Methodological considerations

In our observational studies, systematic errors due to a lack of randomization may affect the validity of our findings. Therefore, we must critically evaluate how selection bias, information bias, confounding, and statistical imprecision may have influenced our findings (Figure 4)⁸⁵.

Figure 4 Association and cause. Modified from Fletcher, Clinical Epidemiology: The Essentials⁸⁵.



Studies II and IV are based on data from the NMSC database. Assessing the completeness and accuracy of the NMSC database is necessary for estimating the usefulness of the data in the NMSC database. **Study III** was conducted to validate the completeness and accuracy of key variables in the database.

Selection bias

Selection bias occurs when the association between the exposure and outcome differs between participants and non-participants in a study¹⁴². In cohort studies, selection bias can arise if the prognosis or risk among participants of the study systematically differs from the prognosis of non-participants. In case-control studies, selection bias arises if the case status is misclassified, or if the association between the exposure risk factor and the risk of NMSC differs systematically between participants and non-participants.

In **Study I**, the cases were identified in the DCR, which has an incomplete registration of NMSCs^{16-18;33}. Selection bias may occur if NMSCs are under-registered due to the favorable prognosis⁹. We cannot rule out that under-registration is influenced by the presence of a history of hip fracture or coexisting chronic diseases. If patients with chronic diseases have more frequent contact with physicians (surveillance bias), this could have lead to better ascertainment and registration of

NMSC in these patients. However, under-ascertainment of NMSC in patients with chronic disease could also occur due to medical attention being focused on the more serious coexisting disease. Both scenarios would introduce bias due to systematic differences in characteristics between those who are selected for the study and those who are not in the study¹⁴³. The first scenario would skew the data on NMSC patients who have poorer health, resulting in an underestimation of the overall effect of a history of hip fracture on NMSC risk. The second scenario would skew the data on NMSC patients towards those with a better health status, leading to a potential over-estimation of the effect¹⁴³. However, the more pronounced inverse association between a history of hip fractures and the risk of BCC in patients with tumors on the trunk or extremities or at multiple sites cannot be explained by this possible bias.

Similarly, patients with a hip fracture may be less mobile and, thus, less likely to go outdoors or to their physician for a skin examination. However, the more pronounced inverse association between a history of hip fractures and risk of BCC in patients with tumors on the trunk or extremities or at multiple sites cannot be explained by this possible bias.

A limitation of **Study III** is the lack of randomization of the two clinics included in the validation study. This limitation may cause *selection bias* if the two selected clinics differed from the other clinics in how they registered data in the database. The clinics were chosen to obtain 15 months of follow-up, and only two clinics had registered data in the database for more than 15 months. The two clinics participating in **Study III** had also participated in the pilot testing of the database. However, the study period of **Study III** did not include the pilot testing phase because changes were made to the questionnaires during pilot testing, and because the completeness may differ in the beginning compared with later registration when the clinics had more experience with the process.

In **Studies II and IV**, the study participants were identified in the NMSC database. Study III revealed an incomplete registration of patients in the NMSC database, and we have not examined whether NMSC patients registered in the database differed from patients who were not registered.

Study IV was conducted as a cohort study. Selection bias may arise if the attendance of participants at follow-up differs systematically from the attendance of non-participants at follow-up, or due to non-random loss to follow-up. This study was restricted to patients treated by dermatologists in an office-based setting because treatment and follow-up in the hospital and by other specialties was not registered in the database. Patients referred to the hospital for treatment may have a more advanced stage NMSC, which may cause bias due to the selection of less advanced tumors in Study III.

⁴⁴

Information bias

Information bias may occur if information collected about a study subject is erroneous¹⁴². This misinformation may result in misclassification of the exposure, outcome, or confounding factors. The misclassification can either be differential (the exposure status is misclassified dependent of the outcome status or vice versa) or non-differential (the exposure status is misclassified independent of the outcome status or vice versa)¹⁴².

In **Study I**, we used a history of hip fracture as a measure of low vitamin D levels. NMSC patients were used as a proxy measure of high sun exposure, causing vitamin D synthesis. We did not have information on vitamin D levels or sun exposure habits for the study subjects. By using these proxy measures of low and high sun exposure, the recall bias of self-reporting measures regarding sunlight exposure can be avoided. However, misclassification may occur by using proxy measures, and we cannot entirely rule out differential misclassification.

In **Study I**, we used socioeconomic information from the IDA database, which are data with high validity¹³⁷. The mean ages of our study populations were high, and information on occupational level and income was obtained for a period of 10 years before diagnosis/index date to build a more accurate picture of the overall occupational and income status.

If information collected about the study subjects is erroneous, information bias may arise¹⁴². This bias can result in misclassification of the exposure, the outcome, or the confounding factors. The misclassification can either be differential or non-differential, depending on its distribution among the compared groups.

In **Studies I and IV**, data on coexisting diseases were collected from the DNPR. Diagnoses of the diseases are of high validity according to the Charlson Index^{139;144}. An advantage of our study is the use of prospectively collected routine data on discharge diagnoses from the DNPR, minimizing information bias.

Study III revealed high accuracy of the prognostic and treatment-related variables, minimizing misclassification of these variables in **Studies II and IV**. However, the incomplete registration of follow-up after treatment may result in a misclassification of the attendance at follow-up in **Study IV**. The lower attendance at follow-up visits in patients with a previous history of skin cancer may be due to differential misclassification. If a patient is treated for new tumors at a follow-up visit, two questionnaires have to be filled out, one with questions concerning the treatment and one concerning the follow-up visit, which may cause incomplete registration for the follow-up visit. In

order to reduce misclassification, we re-analyzed the data excluding patients with more than one registered tumor because patients attending the clinic with a new tumor could increase the likelihood of registering a follow-up of earlier tumors. Less experience in registering data in the database may also have caused a higher completeness of the registration of follow-up visits. Therefore, we re-analyzed the data, restricting it to clinics with the highest number of patients registered in the database. However, both analyses revealed similar results.

In **Study III**, the risk of *information bias* was minimized by systematically reviewing medical records using a standard form. Data were entered into EpiData 3.1, blinded from the data in the NMSC database. Subsequently, the data was compared with the data in the NMSC database. When information registered in the NMSC database disagreed with the data in the medical record, the medical record was reviewed again and any uncertainty discussed and clarified with an independent dermatologist.

Confounding

Confounding, or simply the mixing of effects, is an important issue in observational studies. To influence the association between exposure and outcome, a confounding factor must affect the outcome, and its presence must be unevenly distributed between exposure groups¹⁴². A third and important requirement for confounding factors is that the confounder may not be in the causal pathway between the exposure and outcome¹⁴².

We controlled for confounding in both the design and analysis of each study.

In **Study I**, we controlled for age and gender by matching cases and controls. We also stratified by age and gender, as the effect of these variables may differ based on whether an individual is young versus old or male versus female.

In **Study IV**, we included all patient-, tumors and treatment-factors in the fully adjusted logistic regression model, together with information on the treating clinic.

In **Studies I and IV**, we adjusted for coexisting disease, and in **Study I** we also adjusted for socioeconomic status. We used administrative data from existing registries to control for confounding. In general, any lack of specificity in these routinely recorded data may have reduced our ability to completely adjust for confounding. In addition to the lack of specificity of recorded data, the main disadvantage of register-based studies is the lack of data on lifestyle confounders, such as smoking, obesity, and physical activity, although chronic pulmonary disease, which was

adjusted for, can be used as a proxy measure of smoking. However, the lack of data on potential confounders may not explain the more pronounced inverse association between a history of hip fractures and risk of BCC in patients with tumors on the trunk or extremities or at multiple sites compared to tumors on the head and neck.

Another limitation of **Study I** was the inability to account for medication taken for chronic diseases that may influence the association between exposure and outcome; for example, prednisolone is known to increase the risk of both NMSC and hip fracture.

Precision

We used 95% CIs throughout this thesis to report the precision of the estimates. The width of the CIs indicates the amount of random error in our estimates. As the NMSC database was developed as a part of this PhD, the study material has been limited, which is reflected in wide CIs in the subgroup analyses. However, even in our large study populations of BCC and SCC patients identified in the DCR in Study I, some of the estimates in the subgroups analyses had wide intervals.

Other considerations

Another limitation of **Study III** was the inability to validate information on the cosmetic results due to a lack of this information in the medical record.

Comparison with existing literature

Study I

To the best of our knowledge, only one study has investigated the association between fracture and NMSC¹¹⁵. A Tasmanian study reported a reduced risk of prior NMSC in a fracture cohort using sex-, age-, and calendar year-specific cancer incidence rates in southern Tasmania as a reference¹¹⁵. In contrast, we investigated the association between prior hip fracture and NMSC, and had the opportunity to separately examine the association in BCC and SCC. We also had the opportunity to adjust for coexisting disease and SES. Consistent with the Tasmanian study, we found an inverse association between a history of hip fracture and BCC. However, we did not find an inverse association with SCC. Factors other than sun exposure, such as smoking, chronic disease, and immunosuppression, may play a more significant role in the pathogenesis of SCC compared to

BCC^{66;79;80;83;84;145}, which may explain why we did not find a reduced risk of SCC among patients with a prior history of hip fracture.

Sun exposure resulting in vitamin D synthesis may explain the link between a reduced risk of hip fracture^{112;114;146} and an elevated risk of BCC⁹⁹. Our results are consistent with the finding that self-reported high sun exposure is associated with lower hip fracture risk^{146;147}. However, because we used NMSC patients as a measure of high sun exposure, we can avoid the recall bias of self-reported measures of sunlight exposure.

In our study, we also had the opportunity to stratify our analyses by tumor location. The head and neck make up a small part of the whole body surface area, and exposure of these areas to the sun results in limited vitamin D synthesis¹⁴⁸. In contrast, the trunk and extremities represent a larger surface area of the body, and their exposure to sunlight results in much more vitamin D synthesis¹⁴⁸. Our study suggests that the inverse association with fracture risk was most pronounced for tumors located on the trunk, extremities, and at multiple sites compared to tumors on the head and neck.

Two studies have investigated the association between serum vitamin D and NMSC. In agreement with our findings, Asgari *et al* reported that higher pre-diagnostic serum 25(OH)D levels are associated with an increased risk of subsequent BCC¹¹⁶. In contrast, Tang *et al* reported an inverse association between 25(OH)D levels and NMSC in elderly men¹¹⁷. However, they suggested that their findings may be due to sun avoidance behaviors after NMSC diagnosis because they measured 25(OH)D levels at baseline and recorded the history of skin cancer at baseline or 5 years after baseline.

Study II

Existing data sources are carefully described in the introduction of this thesis (pages 5-12). The NMSC database is unique compared to other data sources. The NMSC database encompasses detailed data on diagnosed tumors, both primary and subsequent, as well as information on the outcome after treatment, as assessed by the dermatologist in terms of recurrence and complication, and the cosmetic result as assessed by both the dermatologist and patient.

Consistent with previous Danish studies, we found that curettage with cautery was the most frequently used treatment^{124;125}. However, NMSC treatment in Denmark differs from management in other countries. In the UK, only 24% of the tumors in 1995 were treated with curettage and cautery, whereas 54% of the tumors were treated with excision¹⁴⁹. The same pattern was seen in a

US study reporting differences in the treatments received in a private dermatology clinic and a Veterans Affairs clinic. Curettage with cautery was used in 23% of the cases in the private clinic and 19% of the cases in the Veterans Affairs clinic; excision in 25% and 48% of cases, respectively; and Mohs surgery in 37% and 25% of cases, respectively. According to guidelines for treatment of NMSC, several treatments may be appropriate in tumors with a low risk of recurrence^{90;91;118-121}. Several factors may influence the choice of treatment, including the experience and training of the dermatologist, the patient's wishes, or economic considerations. A US study based on Medicare data estimated that the lowest treatment cost per patient was obtained with curettage⁵⁰. However, very little research has been done on the effectiveness of the treatment modalities in routine clinical practice^{90;91;93}, and most guidelines refer to outcomes from selected patient groups in a hospital setting^{90;91;93}.

Study III

Accurately registering variables is important for the validity of the data source. Few available NMSC data sources, including the DCR, have used histopathological reports to confirm diagnosis^{7;33;150}. We reviewed medical records and used histopathological reports in the DPR to evaluate the accuracy and completeness of key registered variables, finding high accuracy for prognostic and treatment-related variables. The number of recurrences and complications was small, and the estimates of these variables were imprecise. Only two other NMSC registries have used medical record review for evaluating accuracy. The Southeastern Arizona Skin Cancer Registry reported 97.5% concurrence for all registry information⁷. However, data registration in the registry ended in 1996⁷. A validation of private insurer claims data against medical records using either the registered code for the diagnosis (ICD-9-CM) or the code for the treatment (CPT) in a HMO showed a high PPV of the NMSC diagnosis⁴⁸. However, another health system administrative database owned by the same insurance group and validated against medical records confirm NMSC in less than 50% of the cases using the ICD-9-CM code to identify the patients. However, using both the ICD-9-CM and CPT codes to identify NMSC patients in the database, the PPV was 94.9%⁴⁸.

The modest completeness of the NMSC database must be evaluated and compared with available NMSC data sources. In the DCR, the completeness of incident BCC cases is estimated to be only $50\%^{33}$, and the Southeastern Arizona Skin Cancer Registry reports a completeness of $85\%^{7}$.

In the future, clinics registering data in the NMSC database will receive a list every third month on missing registrations compared to the DPR.

Study IV

Our findings extend the previous research with comprehensive and detailed information on patientrelated factors. No other study had data on actual patient attendance at follow-up. McLoone *et al* and Veien *et al* reported the proportion of patients who attended follow-up in single clinics, but they did not report on factors associated with attendance, and the results were based on small patient numbers^{12;124;125}. Bower *et al* investigated the follow-up practice for well-defined BCC on the face by means of a questionnaire sent to dermatologists in the UK and Ireland¹³². Dermatologists were more likely to offer follow-up to patients with tumors within the H-zone (lips, nose, and eye area) of the face¹³² or those treated with curettage compared to excision¹³². In our study, all patients were offered follow-up for the first year; however, similar to Bower *et al*, patients with tumors on the lips, nose, ears, and in the eye area were more likely to attend follow-up compared to those with tumors in other parts of the head and neck region. In contrast to Bower, we had no information on the dermatologists' attitudes to follow-up; therefore, we cannot comment on provider-related factors that could have influenced attendance.

Main conclusions

Based on the results and an examination of potential bias, confounding factors, and chance in the studies, we drew the following conclusions:

Study I

Our results indicate that patients with a history of hip fracture have a reduced risk of BCC but not a reduced risk of SCC. The inverse association is most pronounced in cases with tumors on the trunk, extremities, or at multiple sites. The correlation between a history of skin cancer and tumor location suggests that sun exposure resulting in vitamin D synthesis may explain the inverse association between hip fracture and BCC.

Study II

We described the development and content of a new population-based database for registering NMSC, Bowen's disease, and keratoacanthoma (the NMSC database). We found that curettage with cautery is the most frequently used treatment modality.

Study III

Overall, the accuracy of variables registered in the NMSC database is satisfactory. However, due to small numbers, the estimates for outcome-related factors are imprecise. The completeness of patient registration and follow-up visits is modest.

Study IV

We found high attendance at follow-up visits within the first year after NMSC treatment. Patients with large tumors or tumors in high risk areas are associated with higher attendance at follow-up visits, whereas comorbidities and older age are associated with lower attendance. Attendance at follow-up visits may not be the highest medical priority among elderly patients or those with concomitant disease because of the relatively favorable prognosis of BCC, whereas patients with high risk tumors have the most to benefit from a follow-up visit because of the increased risk of recurrence.

Perspectives

In study I we find an inverse association between BCC and hip fracture supporting the hypothesis that vitamin D may contribute to the improved survival observed among BCC patients compared to the general population. Study I illustrates how the existing Danish administrative database can be used to further the understanding of NMSC. However, the use of the existing data sources has limitations due to the incomplete registration, as well as lack of clinical details. More detailed data on NMSC and the treatment of NMSC are important for surveillance, prediction of prognosis, improvements in quality of care and treatment, and for research purposes.

Studies II, III, and IV presented in this thesis demonstrate that the NMSC database constitutes a potentially valuable tool for investigating a number of issues that may arise from both clinical and research settings. We described the detailed registration of data in the database, and our study highlights the accuracy of the variables registered. We found, however, that the completeness of registration could be improved. Moreover, in the future, measures will be taken to obtain higher registration completeness.

In August 2010, the database was granted permission to operate as a national clinical database and, in the future, the database will be extended to operate nationwide. A future aim is to invite hospital departments and other specialties treating NMSC to register in the database.

Our results indicate that NMSC treatment in routine clinical practice differs between countries. Data from the NMSC database may in future be used to investigate the effectiveness and cost of NMSC treatment in routine clinical practice, and to map regional variation in NMSC treatment in Denmark. This will provide further understanding of the quality of care for NMSC.

In Denmark, attempts have been made to develop and implement indicators for the quality of the performance of the health care system. Monitoring the performance has, until now, only been done in hospital settings, and the NMSC database is the first clinical database in an office-based setting. As such, the NMSC database has the potential to be a valuable tool for monitoring and facilitating improvements in NMSC care in routine clinical practice. The NMSC database may provide valuable knowledge that can be used to construct evidence-based clinical guidelines for NMSC treatment.

Currently, registering follow-up visits within the first year after diagnosis is mandatory, but followup visits conducted later are registered on a voluntary basis. Guidelines recommend one year of follow-up for low risk tumors. Longer follow-up for all tumors, including low risk tumors, would entail a significant burden to the patients and the health care system. However, by improving the completeness of the registration of treated tumors, long-term follow-up will be possible because any recurrence of a previously treated tumor will be registered in the database when the recurrence is diagnosed and treated.

The value of the NMSC database may prove to be even greater than NMSC databases in other countries because of the unique opportunity to link data on NMSC patients to other Danish population-based and medical data sources. In relation to study I, a future study could investigate serum vitamin D levels among NMSC patients and the general population in a large study population through the link between the NMSC database and the regional Laboratory Information System (LABKA), that contain information on blood samples from the Central Denmark Region.

In conclusion, we have shown that data from the DCR on NMSC can be used to study NMSC. The NMSC database includes detailed clinical data on prognostic-, treatment- and, outcome-related variables, and the data can be used to provide new insight on and further our understanding of the morbidity, public management, and health care costs and effectiveness of the most common cancer in the Caucasian population. Therefore, the NMSC database will be an important resource for future studies on NMSC epidemiology in terms of the etiology, treatment, and prognosis of the disease.

Summary

Non-melanoma skin cancer (NMSC), including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), is the most common malignancy in western countries. NMSC represents a significant challenge in terms of public health management and healthcare costs. However, high quality epidemiological data on NMSC are sparse because NMSC is not routinely registered in cancer registries in most countries. Knowledge is limited on how the most common malignancy is treated in every day clinical practice and how large the burden really is on public health.

The Danish Regional NMSC Dermatology Database (the NMSC database) was established to provide new and detailed data on NMSC, Bowen's disease, and keratoacanthoma diagnosed in dermatology clinics. The NMSC database is an online database containing detailed information on the tumor, prognostic factors, treatment modalities, and the outcome of treatments performed in the dermatology clinics.

This thesis included three studies based on data from the NMSC database. We also conducted one study based on NMSC data from the Danish Cancer Registry. This thesis aims to: 1) examine the association between hip fractures and the subsequent risk of NMSC; 2) develop and describe a database for registering NMSC, Bowen's disease, and keratoacanthoma in dermatology clinics and examine treatment modalities in routine clinical practice; 3) examine the validity of the data in the NMSC database, including the completeness of NMSC registration and the accuracy of key variables in the database; 4) examine predictors of attendance at follow-up after BCC treatment in dermatology clinics.

In **Study I**, we found that a history of hip fracture was associated with a decreased risk of BCC (OR 0.90, 95% CI 0.85-0.94), particularly in cases with tumors on the trunk, extremities, or at multiple sites. We found no association with SCC (OR 1.07, 95% CI 0.98-1.17). Our study showed an inverse association between a history of hip fracture and the risk of BCC, but not the risk of SCC. Sun exposure resulting in vitamin D synthesis may explain the inverse association between hip fracture and BCC. In **Study II**, we described the development and content of a new population-based database for registering NMSC, Bowen's disease, and keratoacanthoma (the NMSC database). Approximately 90% of the registered tumors were BCC tumors, and curettage with cautery was the most commonly used treatment, independent of location and tumor type. In **Study III**, we found that the accuracy of key variables registered in the database is satisfactory, but the completeness of patient registration is modest. The completeness of patient registration was 62%

and 76% based on the Danish National Pathology Registry and medical record review as gold standards, respectively. In **Study IV**, we found that 82% of the patients were registered with at least one follow-up visit within the first year after NMSC treatment. Factors associated with higher attendance included tumors in high-risk areas of the head and neck compared with other head and neck sites (adjusted OR 2.00, 95% CI 1.15-3.48 for overall follow-up) and patients with larger (\geq 20mm) compared with smaller (\leq 5mm) tumors (OR=1.98 (95%CI:0.83-4.57)). Patients with multiple skin cancers had lower attendance than those with no previous tumors (adjusted OR 0.55, 95% CI 0.31-0.98 for overall follow-up). Older patients (>85 years; adjusted OR 0.64, 95% CI 0.33-1.23) and those with any comorbid diseases (OR 0.81, 95% CI 0.56-1.17) were also less likely to attend follow-up visits within the first 15 months.

In conclusion, study I showed that data on NMSC from the Danish Cancer Registry can be used to study NMSC. However, more detailed data are desirable in order to assess more complex health outcomes in patients with NMSC. Our studies showed that the NMSC database has the potential to become a significant resource for epidemiological research of NMSC. Therefore, the NMSC database will be an important resource for future studies on NMSC epidemiology in terms of the etiology, treatment, and prognosis of the disease.

Dansk resume

Non-melanom hudkræft (NMSC), herunder basal celle carcinom (BCC) og pladecellekræft (SCC), er den mest almindelige kræftform i de vestlige lande. Forekomsten er stigende, og vi står overfor et voksende sundhedsproblem. Registreringen af NMSC er mangelfuld, og vi har ikke fuldt overblik over prognosen ved denne kræftform, eller hvorledes den behandles i klinisk praksis, og hvor stor byrden er på folkesundheden.

Den danske regionale dermatologiske NMSC (NMSC databasen) blev opbygget i forbindelse med dette PhD projekt og indeholder en registrering af NMSC, Mb. Bowen og keratoakantom diagnosticeret i dermatologisk speciallæge praksis. NMSC databasen er en online database, hvor detaljerede oplysninger om prognostiske faktorer, behandlingsmetoder, og resultatet af behandlingen registreres.

Denne afhandling omfatter tre studier baseret på data fra NMSC databasen og et studie med NMSC data fra det danske cancer register. Denne afhandling har til formål at: 1) undersøge sammenhængen mellem hoftefraktur og risikoen for NMSC; 2) udvikle og beskrive en database til registrering NMSC, MB. Bowen og keratoakantom og en undersøgelse behandlingen af NMSC i dermatologisk speciallæge praksis, 3) undersøge data kvaliteten i NMSC databasen, herunder komplethedsgraden af NMSC registreringen og nøjagtigheden af de registrerede variabler i databasen; 4) undersøge faktorer af betydning for deltagelse i kontrolbesøg efter BCC behandling. I studie I, fandt vi, at tidligere hoftebrud var forbundet med en nedsat risiko for efterfølgende BCC (OR=0,90; 95% CI 0,85 til 0,94), navnlig gældende for tumorer på trunkus, ekstremiteter, eller multiple lokalisationer. Vi fandt ingen sammenhæng med SCC (OR=1,07, 95% CI 0,98-1,17). Vores studie viste altså en invers sammenhæng mellem tidligere hoftebrud og risikoen for BCC, men ikke for risikoen for SCC. Solen resulterer i D-vitamin syntese, hvilket kan være en forklaring på den inverse sammenhæng. I studie II, beskrev vi udviklingen og indholdet af NMSC databasen. Ca. 90% af de registrerede tumorer var BCC tumorer, og curettage med el-kaustik var det mest almindeligt anvendte behandling, uafhængigt af tumor lokalisation og tumortype. I studie III, fandt vi, at kvaliteten af variabler registreret i databasen var tilfredsstillende, mens komplethedsgraden af patientregistreringen ikke var tilfredsstillende. Komplethedsgraden var hhv. 62% og 76% ved brug af hhv. patologi registeret og journal oplysninger som guld standarder. I studie IV, fandt vi, at 82% af patienterne blev registreret med mindst én opfølgende besøg indenfor det første år efter NMSC behandling. Faktorer forbundet med højere fremmøde inkluderede tumorer i høj-risiko områder i hoved og hals (justeret OR=2,00, 95% CI 1,15-3,48 for mindst et besøg) og patienter med store

tumorer (\geq 20mm) sammenlignet med små (\leq 5mm) tumorer (OR=1.98 (95%CI:0,83-4,57)). Patienter med multiple hudkræft tilfælde havde lavere fremmøde end dem uden tidligere tumorer (justeret OR 0,55, 95% CI 0,31-0,98 for mindst et besøg). Ældre patienter (> 85 år; justeret OR= 0,64, 95% CI 0,33-1,23), og dem med komorbid sygdomme (OR=0,81, 95% CI 0,56-1,17) havde ligeledes lavere fremmøde til opfølgende besøg indenfor de første 15 måneder efter behandlingen. Studie I, viste at NMSC data fra det danske Cancerregister kan bruges til at studere NMSC, men mere detaljerede data er ønskeligt. Vores studier viste, at NMSC database har potentiale til at blive en betydelig ressource for epidemiologisk forskning af NMSC og databasen vil kunne bruges til fremtidige studier af ætiologi, behandling og prognose af sygdommen.

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Appendix

Appendix 1: Treatment questionnaire

Patient's CPR-number:_

Name: _

A. Mark tumor location: Number the tumors: 1-?



	Regional lymphnode metastases	
Distant metastasis	No distant node metastases	
	Distant node metastases	

I Troatmonte		Tumor number				
I. Meatments		1	2	3	4	5
Cryotherapy						
Curettage						
Curettage and cautery/electrodesicca	ition (one cycle)					
Curettage and cautery/electrodesicca	tion (two cycles)					
Excision (4 mm margin)						
Excision (6 mm margin)						
Photodynamic therapy						
Radiotherapy						
5-fluouracil						
Imiquimod creme						
Other treatment, specify:						
Referred to hospital department	Plastic surgery					
	Oncology					
	Other:					
Decided no treatment						
Patient does not want any treatment						

J. Patient's skin?

□ Skintype 1 (Very light, always sunburnt, never tans)

Skintype 2 (Light, easily sunburns, rarely tans)

□ Skintype 3 (Rarely sunburnt, easily tans)

Skintype 4 (Slightly dark glow, never sunburnt, always tan)

□ Skintype 5 (Congenital dark skin, never sunburnt)

□ Skintype 6 (Congenital very dark, never sunburnt)

Skin cancer history

K. Has the patient been diagnosed v	vith skin cancer previ	iously?
□Yes	□ No	
If yes, specify (one or more X):		
Basal cell carcinoma	а	
Squamous cell carci	inoma	
Malignant melanoma	а	
🗆 Unknown tumor type	Э	
□ Other kind, specify:_		
If yes, has the patient been diagnos	sed with skin cancer i	more than once before?
□Yes	□No	
If yes, how many times:		
\Box < 5 time	S	
□5 to 20 t	imes	
□>20 time	es	

L. Histological evaluation		Tumor number						
L. HIStological evaluation	1	2	3	4	5			
Basal cell carcinoma								
Squamous cell carcinoma								
Mb. Bowen								
Keratoacanthoma								
Other type, specify:								
Histological examination has not been made								

M. Diagnosis:	Tumor number						
wi. Diagnosis.	1	2	3	4	5		
Macroscopic							
Surgery							
Clinical examination							
Microscopic							
Histology from primary tumor							
Histology from metastasis							
Histology from primary tumor/metastasis unspecified							
Others							

Appendix 2: Follow-up visit questionnaire

Patient's CPR nr:	Name	:

A. Date of follow up visit:____

B. Are there signs of residal tumor or tumor recurrence in the treated area:		Yes	1	No	
If yes,					
Which tumor(s) still shows signs of activity	Tumor number				
Specify the kind of activity	1	2	3	4	5
Residual tumor					
Tumor recurrence					

c. Have you had a new histological examination performed this time? If yes,		Yes		No		
Specify the kind of cancer found			Tum			
Spechy the kind of cancer found		1	2	3	4	5
Basal cell carcinoma						
Squamous cell carcinoma						
Mb bowen						
Keratoakanthoma						
Other kind, specify						

D. In your opinion, how good is the cosmetic result?

Very satisfactory
Satisfactory
Acceptable
Bad

E. Patient's opinion on the cosmetic result on a scale from 1 to 10: (1= worst possible and 10 = best possible)

Enter patients rating here:_____

Type of complication	Tumor number				
	1	2	3	4	5
Pain					
On the treatment day					
≤7 days after treatment					
>7 days after treatment					
Wound infection					
Bleedings					
Retarded wound heeling > 1 month					
Edema					