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Mortality in cancer patients following a history of squamous cell skin cancer

– A nationwide population-based cohort study –

Research Year Report

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Preface

This project was carried out during my Research Year at the Department of Clinical Epidemiology (DCE) at Aarhus University Hospital. I am very thankful to professor Henrik Toft Sørensen for inviting me to this inspiring department and engaging me in several interesting projects.

I am especially thankful to my supervisors. To Anne, for always being generous with her time to answer my questions with her clinical and epidemiological expertise. To Tim, for always having an open door when I needed help solving statistical or epidemiological problems. To Annette, who took time to co-write the article while she was still on a maternity leave.

I would like to express my deep gratitude to Dóra for helping me with data management and statistical advice. I would also like to express my sincere thanks to the rest of my colleagues at DCE. There is always a warm and friendly atmosphere, and no matter what kind of problem you have there is always someone ready to give you a hand. Especially, I want to thank the girls in the office, Anne and Gitte, for some great times and many good laughs.

I am deeply grateful to my family and friends for their support. In particular, I want to thank my boyfriend and colleague for his love and support both at work and in the everyday life.

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LIST OF ABBREVIATIONS

BCC: Basal cell carcinoma

CCI: Charlson comorbidity index

CI: Confidence interval

CLL: Chronic lymphocytic leukemia

CRS: The Danish Civil Registration System

DCR: The Danish Cancer Registry

DNPR: The Danish National Patient Registry

HIV: Human immunodeficiency virus

ICD: International Classification of Diseases

MRR: Mortality rate ratio

NHL: Non-Hodgkin's lymphoma

NMSC: Non-melanoma skin cancer

SCC: Squamous cell carcinoma

UVR: Ultraviolet radiation

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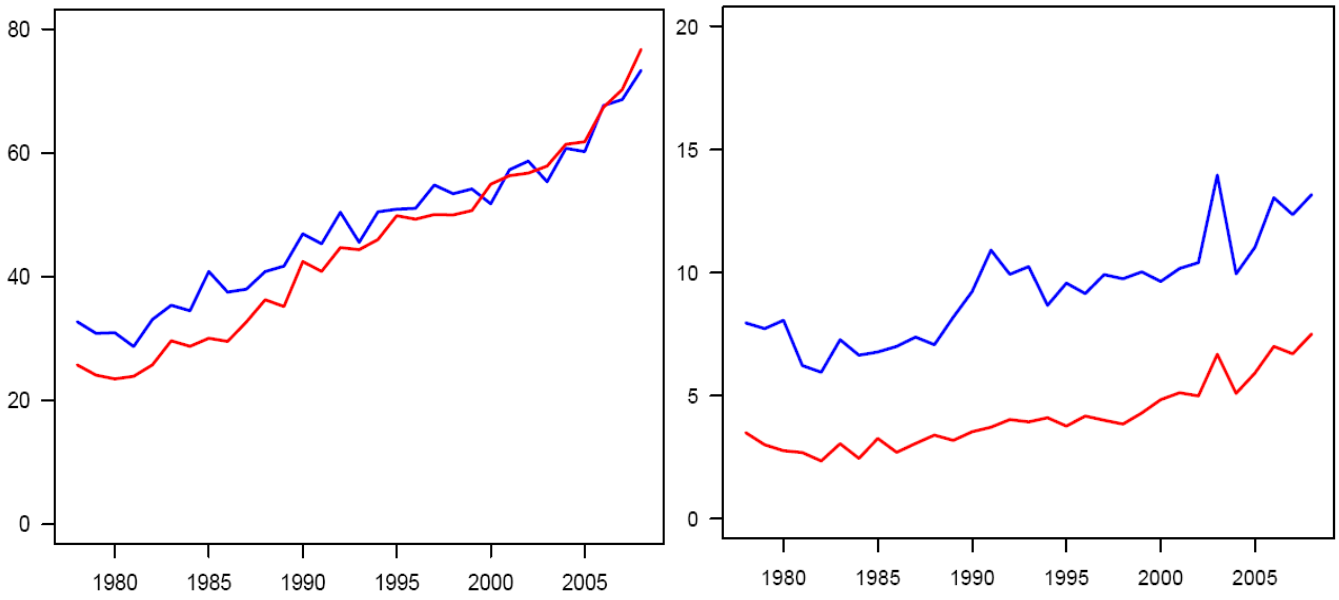
Introduction

The definition and incidence of non-melanoma skin cancer

Non-melanoma skin cancer (NMSC) is the most common cancer among Caucasians and the incidence has been increasing worldwide over recent decades (Figure 1).[1-3] Like the name implies, non-melanoma skin cancer encompasses all skin cancers not originating from the melanocyte including less common types such as cutaneous lymphomas and angiosarcomas. Nonetheless, the term is often used when referring only to the keratinocyte carcinomas, that is, squamous cell carcinoma (SCC) and basal cell carcinoma (BCC).[1] This report focuses on SCC, which is the second most frequent NMSC subtype after BCC.[1]

Figure 1. Age-standardized incidence rate per 100.000 person-years (World Standard Population) for basal cell carcinoma (left) and squamous cell carcinoma (right) among males (blue graph) and females (red graph) in Denmark, 1977-2008.[3]



The risk factors for SCC

Multiple and related risk factors are associated with the pathogenesis of SCC. Genotypic and phenotypic risk factors include light skin, eye and hair color, inability to tan, and benign sun-related skin disorders (*e.g.* actinic keratoses and solar lentigines).[2] The major environmental carcinogen is cumulative lifetime sun exposure.[2] Evidence incriminating sunlight includes the location of tumors on the skin with maximum exposure, a latitudinal gradient in people with the same skin types, and increasing frequency with increasing length of exposure (age).[2, 4] Other environmental risk factors for SCC are pharmacological immunosuppression,[5-7] diseases affecting the immune system (e.g. infection with human immunodeficiency virus (HIV)[8] and non-Hodgkin's lymphoma (NHL))[9], photosensitizing drugs (*e.g.*, psoralen and UVA (PUVA) therapy,[10] diuretics,[11, 12] and fluoroquinolone antibiotics[12]), infection with human papillomavirus,[13-15] and arsenic ingestion.[1, 16]

The prognosis of SCC

Even though SCC incidence is high and increasing, the case-fatality rate is only about 7 per 1,000 cases.[2] Prognosis depends on several factors among which the most important are host immunosuppressive status, lymph-node involvement or distant metastasis, perineural invasion, and the anatomic site, size, and depth of tumor.[2] Despite the good prognosis, morbidity is high and the cost of treatment is expensive.[2] Furthermore, there is an increased risk of developing both subsequent skin cancer[17] and other malignancies compared with the general population,[18-20] and it has been suggested that a history of SCC is also associated with an increased mortality rate for subsequent cancer.[19, 21-24] The explanation for a potentially increased risk and mortality of cancer following SCC is unclear, but an underlying immunodeficiency may be the explanation. This hypothesis will be elaborated in the following.

Immune function and SCC

Several risk factors may influence the association between immune function and SCC. The cumulative UVR exposure is especially interesting since it is DNA-damaging (*e.g.*, formation of pyrimidine dimers)[1] and also induces immunosuppression.[25, 26] Studies in photoimmunology have shown that UVR energy is absorbed by photoreceptors (*e.g.*, DNA) in the skin, which results in an alteration of the antigen-presenting function of dendritic cells either directly or indirectly by initiating a cascade of down-regulatory signals involving transcription factors, cytokines and other biological response modifiers (*e.g.*, IL-10, neuropeptides and neuroendocrine hormones).[25] Together with UVR-induced suppressor T cells, this cascade finally results in cellular (T cell) immune incompetence.[25] This reduced immune function may be observed both locally and systemically and it is more pronounced in patients with previous skin cancer than in the general population.[25, 26] The exact temporal extent of the immunosuppression is unknown, but observations of decreasing cellular immunity[27, 28] and number and function of Langerhans cells with age[29] supports a link between cumulative UVR and immunosuppression. Moreover, the pharmacologically induced suppression of the CD4+ lymphocytic response in transplant patients increases the risk of UVR-induced SCC[30] predominantly in adults,[31] which may reflect differences between adult and pediatric patients with regard to cumulative UVR exposure before transplantation.

These findings suggest that SCC may be regarded as a marker of underlying immunosuppression in the patient. This immunosuppression may compromise normal immune surveillance against nascent tumor cells,[27, 28] which could explain an association between SCC and increased risk and mortality of cancer.

SCC and the prognosis of subsequent cancer

To date, only five studies have investigated whether a history of SCC affects prognosis of subsequent cancer.[19, 21-24] The results and details of the studies are presented in Table 1. Overall, they found that cancer patients with previous SCC had worse prognosis. None of the studies, however, adjusted for important prognostic factors such as comorbidity and cancer treatments, which calls into question the validity of their results.

Table 1. Studies of mortality in cancer patients following a history of squamous cell carcinoma (SCC)

Authors, country	Cancers studied (no. of SCC patients)	Risk estimates	Covariates	Results						Comments
				Lung	Colon	Rectum	Breast	Prostate	NHL	
Askling *et al.*,[21] Sweden	NHL (223), colon (302), breast (209), prostate (654), and lung cancer (272)	Mortality rate ratios (95% CI)	Age, gender, calendar period	1.29 (1.01, 1.65). Only includes patients who survived ≥1 year	1.24, (1.09, 1.41)	—	1.19 (1.004, 1.42)	1.17 (1.06, 1.28)	1.33 (1.14, 1.54)	For death from breast cancer only women <70 years old were affected (MRR 1.37, 95% CI: 0.97, 2.36).
Hjalgrim *et al.*,[22] Denmark	NHL (36) and colon cancer (64)	Mortality rate ratios (95% CI)	Age, gender, calendar period, stage	—	1.60 (1.06-2.40)	—	—	—	1.75 (0.98-3.13)	Estimates are for persons aged ≥80 years. No excess mortaliy was found in those ≥80 years. Mortality tended to be higher among those with <1 year between diagnoses.
Toro *et al.*,[23] Sweden	CLL (111)	Mortality rate ratios (95% CI)	Age, gender, calendar period	—	—	—	—	—	CLL: 1.86 (1.46-2.36)	
Kahn *et al.*,[24] U.S.	35,062 patients with and 1,061,844 without a history of NMSC were followed until death from any cancer.	Mortality rate ratios (95% CI)	Age, gender, race, education, smoking, obesity, alcohol use, and other conventional risk factors.	Men: 1.37 (1.25-1.50); Women: 1.46 (1.26-1.68),	Men: 1.05 (0.88-1.25; Women: 1.02 (0.81-1.29)	Men: 0.90 (0.56-1.44); Women: 1.09 (0.58-2.06)	1.34 (1.11-1.63)	1.28 (1.11-1.47)	Men: 1.32 (1.03-1.69); Women: 1.50 (1.10-2.05)	Did not differentiate between squamous cell carcinoma and basal cell carcinoma.
Nugent *et al.*,[19] Canada	1,317 cancer patients with history of SCC	Standardized mortality rate ratios (95% CI)	Age, gender	Men: 1.10 (0.93-1.29); Women: 1.55 (1.05-2.20)	Men: 1.15 (0.85-1.53); Women: 1.58 (0.99-2.39)	Men: 1.18 (0.76-1.75); Women: 4.05 (1.94-7.45)	1.45 (1.00-2.02)	1.07 (0.91-1.27)	Men 0.92 (0.62-1.33); Women: 1.97 (1.08-3.31)	Survival was censored at age of 90 years to control for people with missing death date.

NHL: non-Hodgkin's lymphoma
CLL: chronic lymphocytic leukemi

Objective

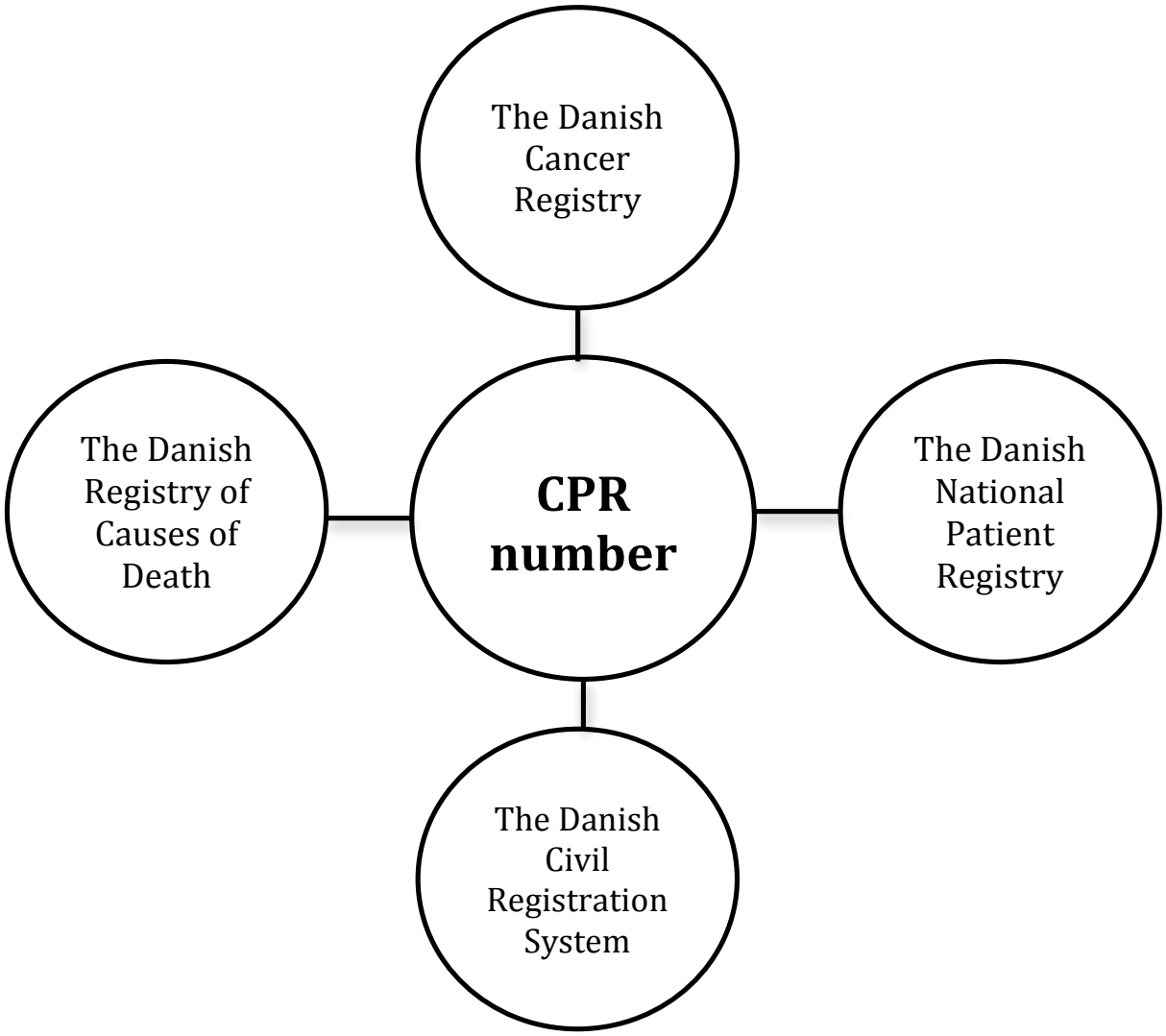
The objective of this study was to examine whether a history of SCC has prognostic impact in patients with a subsequent cancer diagnosis taking into account comorbidity and cancer treatments. We chose to include the most frequent cancers, that is, cancer of the lung, colon, rectum, breast and prostate. Furthermore, we included non-Hodgkin's lymphoma (NHL) given its strong association with immune function.

Material and methods

Study design and data sources

We designed the study as a nationwide cohort study based on Danish national medical databases, which cover the entire Danish population of 5.6 million inhabitants. We linked all registries using the unique 10-digit central personal registration (CPR) number assigned to every Danish citizen at birth and to residents at immigration (Figure 2).[32, 33] All associated ICD codes are provided in the Appendix.

Figure 2. Linkage of the Danish national medical databases used in the study



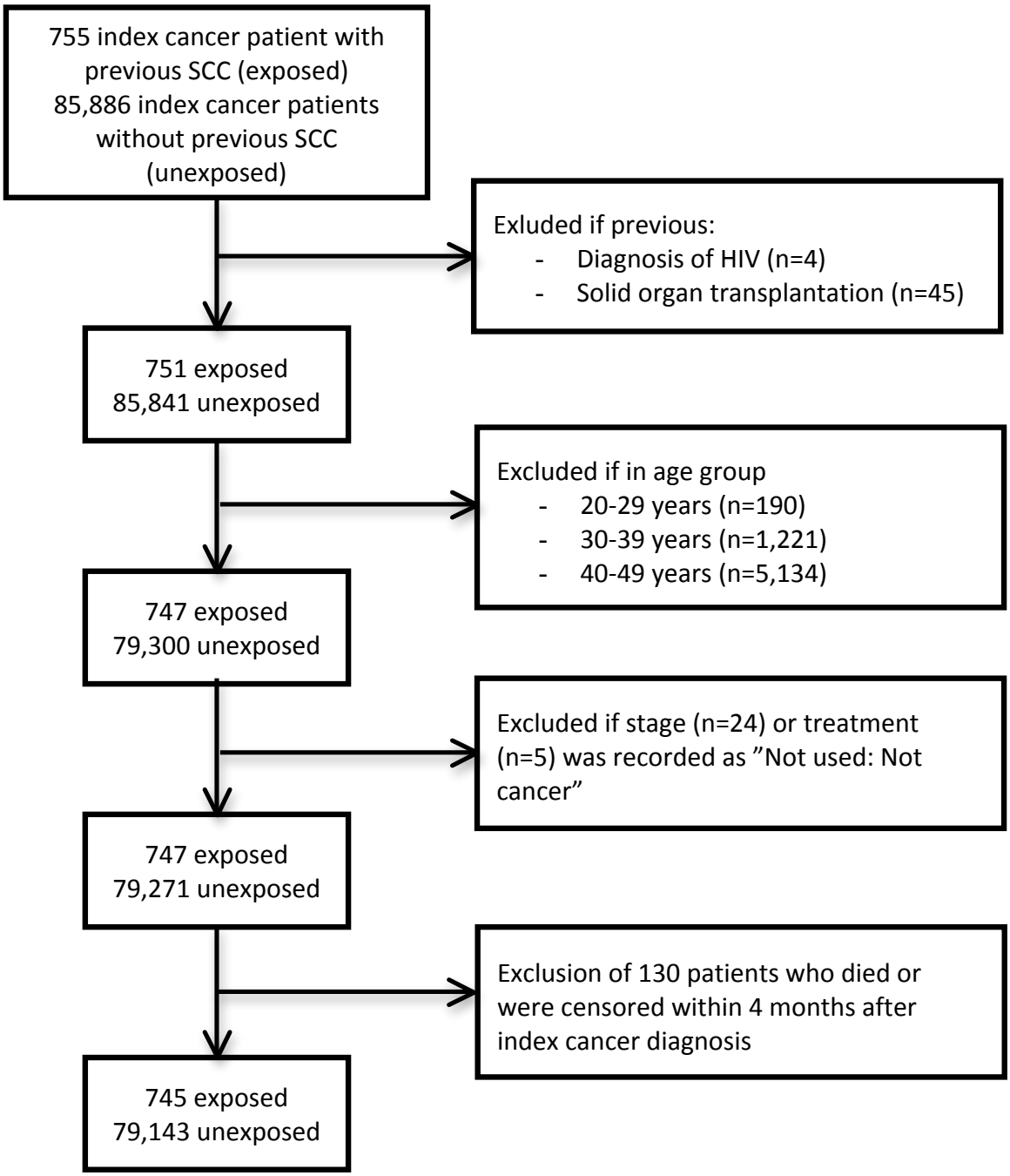
The Danish Cancer Registry

The Danish Cancer Registry (DCR) contains records of all incident cases of malignant neoplasms in Denmark since 1943. Reporting to the registry became mandatory 1 January 1987. Files of the registry provide details on morphology, histology, and stage of cancer at the time of diagnosis.[33, 34] Through 2003, information on initial cancer therapies within four months of diagnosis was also included. Tumors were classified according to the 7th revision of the *International Classification of Diseases* (ICD-7) in 1943 through 2003, and according to the topography and histology codes of the first version of the *International Classification of Diseases for Oncology* (ICD-O-1) in 1978 through 2003.[33] From 1 January 2004 and onwards, tumors are classified according to ICD-10 and ICD-O-3. In addition, tumor diagnoses in the period 1 January 1978 to 31 December 2003 have been converted to ICD-10 and ICD-O-3 through translation of the ICD-O-1 codes.[33]

We used the DCR to identify all patients aged 20 to 99 years with a first diagnosis of SCC and a subsequent index cancer diagnosis of NHL (n=57), or cancer of the lung (n=179), colon (n=138), rectum (n=78), breast (n=117), or prostate (n=186), occurring in the month after a SCC diagnosis or later (exposed patients). Given abundant data in the DCR, in combination with the fact that our focus was survival following the most common cancers in Denmark, we decided that for each selected cancer patient with a history of SCC, we would randomly choose approximately 100 patients with the same index cancer but without preceding SCC (unexposed patients). This procedure resulted in the identification of 7,569 unexposed patients with NHL, 20,218 with lung cancer, 15,589 with colon cancer, 7,534 with rectal cancer, 13,513 with breast cancer, and 21,463 with prostate cancer.

A flowchart of the selection process is presented in Figure 3. Initially, we aimed to include HIV diagnosis and previous solid organ transplantation as a measure of immune function, but due to small numbers of patients with a history of SCC in these categories, we excluded all patients with HIV or previous solid organ transplantation. For the same reason, we also excluded all patients in age groups 20-29, 30-39, and 40-49 years, and we combined age groups 50-59 and 60-69 years. Furthermore, we excluded patients with records stating "Not used: Not cancer" for the variable of stage or treatment. 130 patients who had died or were censored at the start of follow-up were also excluded.

Figure 3. Flowchart of the selection process



The Danish Civil Registration System

We used the Danish Civil Registration System (CRS) to retrieve information on all-cause death and emigration. The CRS was established on April 2 1968, and contains information on CPR-number, name, gender, date and place of birth, residence, date of death and emigration. Information on vital status is updated on a daily basis.[32]

The Danish Registry of Causes of Death

The Danish Registry of Causes of Death contains information on all deaths in Denmark since 1943.[33, 35] Since 1871, the Danish law states that a death certificate should be completed in case of any death occurring in Denmark. Only physicians are permitted to fill in the death certificate, which consists of a civic information part and a medical information part. The civic information part includes general information such as CPR number and home address. The medical information part contains information on one underlying, and up to three immediate causes of death based on ICD-8 diagnostic codes through 1993 and ICD-10 thereafter. Furthermore, results from post-mortem examinations such as autopsy or toxicological reports are recorded.

We used the cause of death reported on the death certificate grouped into 14 categories as defined by the National Board of Health.[36] If any of the causes on the death certificate were a malignancy, we used that as the cause of death. If not, the cause of death was coded as the last immediate cause leading to death.

The Danish National Patient Registry

The Danish National Patient Registry (DNPR) provides information about all inpatient admissions to somatic hospitals since 1977, and all outpatient and emergency admissions since 1995.[33, 37] The files contain information on dates of admission and discharge, hospital and department, diagnosis codes and surgical procedures. Each admission is registered by one primary diagnosis and up to 19 secondary diagnoses according to the ICD-8 diagnostic codes through 1993 and the ICD-10 revision thereafter. From 1977 through 1995, surgical information was coded according to a Danish classification of surgical procedures, which changed thereafter to a Danish version of the NOMESCO (Nordic Medico-Statistical Committee) Classification of Surgical Procedures.

We used the DNPR to obtain information on comorbid diseases and categorized the level of comorbidity by using the Charlson Comorbidity Index (CCI).[38] The CCI is an extensively studied and validated instrument that can be used to predict the risk of death from comorbid diseases, by covering and weighing 19 major chronic disease categories based on the relative risk of dying.[38, 39] We computed the CCI score for each study subject based on the complete hospital discharge history

for at least 5 years before index cancer diagnosis, and grouped it into three levels: Low=0, medium=1-2, and high>2.

According to our hypothesis, SCC is associated with poor prognosis in cancer patients due to underlying immune incompetence. We would therefore expect diseases involving the immune system or immunosuppressive therapies to be more frequent in patients with a history of SCC. To examine this, we also included a list of autoimmune diseases, as a proxy measure of immune function.

Statistical analysis

Follow-up

To include information on initial cancer therapies, follow-up started four months after index cancer diagnosis, and continued until death, emigration, diagnosis of SCC in patients without that history at index cancer diagnosis, end of follow-up (31 December 2008), or a maximum of 10 years, whichever came first.

Descriptive data

We computed the frequency and proportion of demographic and medical variables, the number of deaths and amount of accumulated person-time within each cohort, stratified by whether or not they had a preceding diagnosis of SCC.

Mortality

We computed crude mortality rate ratios (MRRs) with 95% confidence intervals (95% CIs) associating a history of SCC with mortality. Furthermore, we constructed Kaplan-Meier plots for each index cancer stratified on history of SCC and tested their differences using log-rank and Wilcoxon tests.

We used Cox proportional hazard regression to estimate adjusted MRRs with 95% CIs adjusting for age group (50-69, 70-79, 80-89, 90-99 years), a variable that calculated the midpoint of the age group divided by exact age for each individual, gender, CCI (low, medium, high), calendar period (1982–1986, 1987–1991, 1992–1996, 1997–2001, 2002–2003), a history of autoimmune disease (yes/no), stage (localized, regional, distant, unknown/missing), and the following index cancer treatments: no/symptomatic treatment, chemotherapy, radiation therapy, hormone therapy, operation, and other/missing treatment. To examine the presence of effect modification, we stratified the model on age groups, gender, CCI, and a history of autoimmune disease. We also stratified mortality rates on time between SCC and index cancer diagnoses. Next, we fitted a reduced model

without adjustment for stage and treatment since we hypothesized that they may be on the causal pathway linking SCC to poor prognosis. That is, decreased immune surveillance may cause faster progression of the cancers and thereby more advanced stage at diagnosis, which in turn affects the choice of treatment. In a subanalysis, we found no substantial difference between the phenotypic variant chronic lymphocytic leukemia and other NHL types and therefore reported the pooled results. All analyses were performed for both all-cause death and death from cancer within each index cancer and overall. 476 persons, who were registered as dead in the CRS, but not in the Danish Registry of Causes of Death, were censored at the date of death in the analysis for death from cancer. They did not differ from the total population with regard to exposure. Finally, we assessed the assumption of proportional hazards by graphical examination of log-log plots against log-time and found it not to be violated.

Secondary analyses

After 2003, information on cancer treatments was not available. However, treatment only affected estimates for lung and breast cancer mortality by increasing their MRRs about 7%. We therefore extended the enrollment period from 1982 through 2008, to examine the associations for the other index cancers with greater power, but without adjustment for treatment.

A SCC diagnosis shortly after index cancer diagnosis may still be a marker of poor prognosis, causing us to underestimate the effect by including such patients in the unexposed group. We therefore repeated our analysis after excluding unexposed patients receiving an SCC diagnosis within two years after index cancer diagnosis, which did not change the estimates.

Main results

Overall, we included 745 index cancer patients with and 79,143 without a history of SCC. The distribution of characteristics within the index cohorts is presented in Table 2, which shows that SCC patients were older at index cancer diagnosis, were more frequently men, had their index cancer diagnosis in a more recent calendar period, and had higher comorbidity.

Mortality

Overall, a history of SCC was associated with an increased relative rate of death from cancer (MRR 1.13, 95% CI: 1.04, 1.23) (Table 3). When examining index cancers separately, increased MRRs were found for cancer of the lung (MRR 1.23, 95% CI: 1.05, 1.43), colon (MRR 1.13, 95% CI: 0.92, 1.40), rectum (MRR 1.29, 95% CI: 1.00, 1.67), breast (MRR 1.09, 95% CI: 0.82, 1.43), and NHL (MRR 1.09, 95% CI: 0.81, 1.47). There was no increased rate of dying of prostate cancer (MRR 0.99, 95% CI: 0.83, 1.18). The associations were not modified in the stratified analysis (data not shown).

History of autoimmune disease

Index cancer patients with a history of SCC had more frequently a history of any autoimmune disease (Table 2). However, stratification by and adjustment for this variable revealed neither effect modification nor confounding. We had insufficient power to examine effects for subgroups of autoimmune diseases.

Impact of prognostic factors

After including all other covariates, adding comorbidity to the model resulted in a 7% attenuation of the MRR for NHL, but had no effect in the remaining cancers. Adjusting for stage did not affect the results, while adjusting for cancer treatment had an impact in lung and breast cancer in the sense that it raised their MRRs by approximately 7%.

The secondary analysis with extended enrollment period resulted in no substantial change for prostate (MRR 1.03, 95% CI: 0.88, 1.21) and colon cancer (MRR 1.10, 95% CI: 0.90, 1.33. An increase in the MRR was observed for rectal cancer (MRR 1.43, 95% CI: 1.13, 1.81) and NHL (MRR 1.23, 95% CI: 0.96, 1.57).

Table 2. Selected characteristics of persons diagnosed with an index cancer (cancer of the lung, colon, rectum, breast, prostate, or non-Hodgkin's lymphoma (NHL)) in Denmark 1982-2003, by history of squamous cell carcinoma (SCC)

Characteristics	Lung cancer		Colon cancer		Rectal cancer	
	+ SCC (%)	– SCC (%)	+ SCC (%)	– SCC (%)	+ SCC (%)	– SCC (%)
Total	175	18,662	138	14,647	77	7,089
Gender						
Men	140 (80)	11,673 (63)	87 (63)	6,592 (45)	60 (78)	4,086 (58)
Women	35 (20)	6,989 (37)	51 (37)	8,055 (55)	17 (22)	3,003 (42)
*Age group (years)**						
50-69	49 (28)	11,471 (61)	23 (17)	5,968 (41)	15 (19)	3,383 (48)
70-79	82 (47)	5,895 (32)	48 (35)	5,479 (37)	34 (44)	2,487 (35)
80-89	41 (23)	1,241 (6.7)	59 (43)	2,958 (20)	22 (29)	1,107 (16)
90-99	3 (1.7)	55 (0.3)	8 (5.8)	242 (1.7)	6 (7.8)	112 (1.6)
Calendar period†						
1982-1986	19 (11)	3,798 (20)	12 (8.7)	3,023 (21)	11 (14)	1,565 (22)
1987-1991	25 (14)	3,866 (21)	26 (19)	3,219 (22)	15 (19)	1,557 (22)
1992-1996	47 (27)	4,101 (22)	35 (25)	3,324 (23)	22 (29)	1,578 (22)
1997-2001	66 (38)	4,832 (26)	49 (36)	3,549 (24)	17 (22)	1,683 (24)
2002-2003	18 (10)	2,065 (11)	16 (12)	1,532 (10)	12 (16)	706 (10)
Comorbidity level‡						
Low	81 (46)	12,081 (65)	81 (59)	10,806 (74)	54 (70)	5,477 (77)
Moderate	69 (39)	5,306 (28)	47 (34)	3,221 (22)	18 (23)	1,365 (19)
High	25 (14)	1,275 (6.8)	10 (7.3)	620 (4.2)	5 (6.5)	247 (3.5)
Any autoimmune disease	13 (7.4)	854 (4.6)	7 (5.1)	627 (4.3)	4 (5.2)	244 (3.4)
Survival time (years)						
Median	0.53	0.61	2.11	3.50	2.19	3.29
Lower quartile	0.20	0.23	0.70	0.96	0.94	1.13
Upper quartile	1.02	1.50	5.68	8.30	5.21	7.78
Time between diagnoses (years)§						
<1	23 (13)	–	23 (17)	–	10 (13)	–
1-4	55 (31)	–	46 (33)	–	26 (34)	–
>4	97 (55)	–	69 (50)	–	41 (53)	–
Stage						
Localized	62 (35)	5,663 (30)	62 (45)	7,447 (51)	42 (55)	3,639 (51)
Regional	47 (27)	5,993 (32)	49 (36)	4,627 (32)	17 (22)	2,021 (29)
Distant	38 (22)	4,321 (23)	13 (9.4)	1,844 (13)	7 (9.1)	777 (11)
Unknown/ missing	28 (16)	2,685 (14)	14 (10)	729 (5.0)	11 (14)	652 (9.2)
Treatment of index cancer‖						
No or symptomatic	94 (54)	7,513 (40)	8 (5.8)	575 (3.9)	11 (14)	459 (6.5)
Chemotherapy	16 (9.1)	4,012 (22)	3 (2.2)	1,010 (6.9)	1 (1.3)	258 (3.6)
Radiation	23 (13)	3,165 (17)	1 (0.72)	116 (0.79)	1 (1.3)	450 (6.4)
Operation	31 (18)	4,809 (26)	130 (94)	13,812 (94)	63 (82)	6,377 (90)
Hormone therapy	0 (0.00)	48 (0.26)	0 (0.00)	13 (0.090)	0 (0.00)	6 (0.08)
Missing/other	13 (7.4)	663 (3.6)	0 (0.00)	158 (1.1)	2 (2.6)	82 (1.2)

	Breast cancer		Prostate cancer		NHL¶	
	+ SCC (%)	– SCC (%)	+ SCC (%)	– SCC (%)	+ SCC (%)	– SCC (%)
Total	113	10,418	186	21,364	56	6,963
Gender						
Men	–	–	186 (100)	21,364 (100)	46 (82)	3,896 (56)
Women	113 (100)	10,418 (100)	–	–	10 (18)	3,067 (44)
*Age group (years)**						
50-69	25 (22)	6,298 (60)	18 (9.7)	7,014 (33)	11 (20)	3,253 (47)
70-79	38 (34)	2,569 (25)	83 (45)	9,423 (44)	21 (38)	2,492 (36)
80-89	40 (35)	1,369 (13)	77 (41)	4,61 (22)	20 (36)	1,130 (16)
90-99	10 (8.9)	182 (1.8)	8 (4.3)	308 (1.4)	4 (7.1)	88 (1.3)
Calendar period†						
1982-1986	6 (5.3)	1,866 (18)	20 (11)	3,825 (18)	8 (14)	1,261 (18)
1987-1991	18 (16)	2,029 (19)	30 (16)	4,562 (21)	10 (18)	1,392 (20)
1992-1996	28 (25)	2,469 (24)	39 (21)	4,333 (20)	13 (23)	1,659 (24)
1997-2001	44 (39)	2,806 (27)	69 (37)	5,700 (27)	15 (27)	1,876 (27)
2002-2003	17 (15)	1,248 (12)	28 (15)	2,944 (14)	10 (18)	775 (11)
Comorbidity level‡						
Low	77 (68)	8,406 (81)	106 (57)	14,554 (68)	28 (50)	5,183 (74)
Moderate	29 (26)	1,667 (16)	58 (31)	5,558 (26)	20 (36)	1,517 (22)
High	7 (6.2)	345 (3.3)	22 (12)	1,252 (5.9)	8 (14)	263 (3.8)
Any autoimmune disease	9 (8.0)	437 (4.2)	9 (4.8)	853 (4.0)	5 (8.9)	322 (4.6)
Survival time (years)						
Median	4.93	6.57	2.97	3.07	2.41	3.50
Lower quartile	2.12	3.22	1.18	1.26	0.68	1.34
Upper quartile	7.97	10	5.09	5.94	5.27	6.63
Time between diagnoses (years)§						
<1	15 (13)	–	20 (11)	–	9 (16)	–
1-4	34 (30)	–	73 (39)	–	26 (46)	–
>4	64 (57)	–	93 (50)	–	21 (38)	–
Stage						
Localized	55 (49)	4,970 (48)	63 (34)	9,053 (42)	4 (7.1)	482 (6.9)
Regional	33 (29)	3,897 (37)	11 (5.9)	1,441 (6.7)	2 (3.4)	497 (7.1)
Distant	6 (5.3)	526 (5.1)	39 (21)	5,297 (25)	8 (14)	1,039 (15)
Unknown/ missing	19 (17)	1,025 (9.8)	73 (39)	5,573 (26)	42 (75)	4,945 (71)
Treatment of index cancer‖						
No or symptomatic	1 (0.88)	356 (3.42)	35 (19)	3,283 (15)	25 (45)	2,847 (41)
Chemotherapy	8 (7.1)	1,236 (12)	0 (0.00)	164 (0.77)	18 (32)	3,234 (46)
Radiation	12 (11)	2,336 (22)	7 (3.8)	939 (4.4)	6 (11)	473 (6.8)
Operation	97 (86)	9,492 (91)	99 (53)	13,210 (62)	1 (1.8)	151 (2.2)
Hormone therapy	25 (22)	2,763 (27)	28 (15)	3,564 (17)	0 (0.00)	19 (0.27)
Missing/other	2 (1.8)	79 (0.76)	25 (13)	2,078 (9.7)	7 (13)	625 (9.0)

*Age at index cancer diagnosis. †Calendar period of index cancer diagnosis. ‡Three levels of comorbidity were defined based on Charlson index scores of 0 (low), 1-2 (medium), and >2 (high). §Time between SCC and index cancer diagnoses. ‖Numbers do not add up to 100% since some patients may receive a combination of therapies. ¶Includes the phenotypic variant chronic lymphocytic leukemia

Table 3. Mortality rate ratios of cancer with 95% confidence intervals, associated with prior squamous cell carcinoma in persons diagnosed with an index cancer (cancer of the lung, colon, rectum, breast, prostate, or non-Hodgkin's lymphoma (NHL)) in Denmark 1982-2003

	Unadjusted MRR	Adjusted MRR*
Lung cancer	1.27 (1.09, 1.48)	1.23 (1.05, 1.43)
Colon cancer	1.31 (1.06, 1.61)	1.13 (0.92, 1.40)
Rectal cancer	1.53 (1.19, 1.98)	1.29 (1.00, 1.67)
Breast cancer	1.37 (1.05, 1.81)	1.09 (0.82, 1.43)
Prostate cancer	1.11 (0.93, 1.32)	0.97 (0.81, 1.15)
NHL†	1.46 (1.09, 1.96)	1.09 (0.81, 1.47)
Index cancers combined	1.24 (1.14, 1.35)	1.13 (1.04, 1.23)

*All estimates are adjusted for age group, age group divided by exact age for each individual, gender, Charlson comorbidity index (low, medium, high), calendar period (1982-1986, 1987, 1991, 1992-1996, 1997-2001, 2002-2003), history of any autoimmune disease (yes/no), stage (localized, regional, distant, or unknown/missing), and the following index cancer treatments: no/symptomatic, chemotherapy, radiation therapy, hormone therapy, operation, or other/missing treatment.

†Includes the phenotypic variant chronic lymphocytic leukemia

Strengths and weaknesses

When discussing strengths and weaknesses of a study, the evaluation of possible biases is central. Bias is a systematic departure of the results from the true values and can be divided into (1) selection bias, (2) information bias, and (3) confounding, based on how it arises.[40, 41] In the following we will define and discuss these in relation to our study.

Selection bias

Selection bias occurs when the association under interest differs for participants and non-participants.[40, 41] In our study this bias would arise if non-participants (non-registered cases) were less likely to be registered than participant (registered cases) due to some factor that affects both exposure (SCC) and outcome (death from cancer). Given our design (nationwide population-based cohort study) and the fact that Denmark has a homogenous population with a tax-supported health system guaranteeing free health care to all residents, we find selection bias unlikely.

Selection bias could also occur if the rate of loss to follow-up was different in patients with vs. patients without a history of SCC. However, at the end of follow-up only 0% and 0.09% of patients with and without previous SCC respectively had been lost to follow-up due to emigration, annulment of CPR number, or disappearance. Given this low number, we do not find such selection bias likely.

Information bias

Information bias results from erroneous information about study variables.[40, 41] When conducting registry-based research, it is thus important to assess the quality of the registry data. In our study, information bias may have affected exposure, outcome, and covariates.

Exposure

Even though the Danish Cancer Registry is close to complete for most malignancies,[34] NMSC is probably underreported.[18, 42] Reasons for this underreporting may be the high incidence of NMSCs burdening the systems and the high cure rate that may cause physicians to consider it trivial.[43] Our exposure measure may therefore have been subject to misclassification. However, we find it unlikely that mortality of a malignancy occurring later in time would affect misclassification of SCC. This argument is supported by a study of differences between incident and subsequent cases of NMSC with regard to 10-year mortality that found a 25% incompleteness of SCC, which was non-differential in mortality.[42] At the most, this bias would cause us to underestimate the association between SCC and cancer mortality.

Outcome

Misclassification of cause of death may be possible. The Danish Registry of Causes of Death has varying validity for different causes of death, although it is almost complete for deaths from cancer.[35, 44, 45] The major problem with the registry is that even though the causes may be accurate, the sequence of events might be incorrect.[45] To avoid this problem, we regarded cause of death as cancer if any cause on the death certificate was a malignancy. Furthermore, we repeated all analyses for all-cause death by using the civil registration system, which is virtually complete.[32] This change in outcome resulted in no change or a slight attenuation of the MRRs for some index cancers, but they were not substantially different from the cancer-specific MRRs. This finding suggests that there may be some limitations with the Danish Registry of Causes of Death, or that for some index cancers the unexposed cohort died for some causes other than cancer.

Surveillance bias

Surveillance bias might have caused an attenuation of our results if preceding SCC is associated with increased medical surveillance leading to earlier diagnosis, and hence, better prognosis. In accordance with Danish Guidelines on follow-up in SCC patients,[46] a study of NMSC and risk of subsequent cancer found no evidence of more intensive surveillance for internal malignancies,[18] implying that surveillance bias is not a major problem in our study. In our data, we found no substantial difference between mortality rates stratified on time between SCC and index cancer diagnoses. Moreover, we assessed the associations without restricting follow-up to 10 years. The survival time then ranged from 0 to 26.63 years, and still estimates were unaffected.

Autoimmune diseases

The low number of observations limited the analysis of associations for subtypes of autoimmune diseases, and since the degree of immunosuppression varies with severity and type of autoimmune disease "a history of any autoimmune disease" may be an imperfect reflection of immunosuppression. Furthermore, information on a history of autoimmune disease may be underreported, especially in the mild cases. These limitations prevent us from ruling out a differential effect in people with autoimmune disease.

Comorbidity, treatment, and stage

Our study is the first to examine whether a history of SCC is associated with increased mortality following cancer when adjusting for comorbidity and cancer treatments.[19, 21-24] We found that both comorbidity and treatment had no or only a slight effect on our results. However, this finding

depends on the quality of our information on these variables. Since the development of the CCI in the 1980s, prognosis for some of the comorbid diseases has changed radically, with AIDS as the most striking example. Even though, we excluded this patient group our results may be subject to some residual confounding by comorbidity.

As mentioned (page 16 Statistical analysis), we had concerns of whether stage and treatment were intermediates linking SCC to poor prognosis. However, adjusting for stage and treatment did not cause an attenuation of the results suggesting that they are only weak intermediates. Nevertheless, it is interesting that missing information and no/symptomatic treatment was more frequent in SCC patients (page 18-19 Table 2). The reason for this finding is unknown, but it may be that these patients for some reason, *e.g.* presence of comorbid diseases and older age, are more complex. Another explanation could be that these patients are actually undertreated, which would be a problem, especially given our finding of an increased mortality in patients with previous SCC.

Confounding

Confounding, or "mixing of effects," occurs when a factor that is associated with outcome is unequally distributed between exposed and unexposed.[40, 41]

Confounding by lifestyle factors

We had no information on lifestyle factors such as smoking, diet, or exercise, which may explain part of the association that we found.[18, 47-53] For example, smoking is associated with SCC,[18, 47-53] and although lifestyle factors are not well established as factors related to cancer mortality,[52-57] we cannot rule it out as a confounder to explain part of the increased mortality that we found. However, in the study by Kahn *et al.* authors adjusted for lifestyle factors and the adjustment had no effect on their estimates. Furthermore, even if smoking is associated with SCC we would not expect it to affect our results for lung cancer, since most lung cancer patients probably smoke regardless of SCC history.

Discussion in relation to the existing literature

Our results are consistent with those of previous studies that, overall, found increased mortality rates in cancer patients with a history of SCC.[19, 21-24] When examining index cancer types individually, there are, however, some inconsistencies with previous studies (page 9 Table 1). Askling *et al.*, Kahn *et al.*, and Nugent *et al.* included prostate and breast cancer. In all three studies an increased mortality rate of 19-45% was observed among breast cancer patients with a history of SCC. In comparison we only found a 9% increase. In contrast to Askling *et al.* and Kahn *et al.*, we found no increased rate of death from prostate cancer.

The most consistent finding is the increased mortality rate in NHL patients with previous SCC,[19, 21-24] although Toro *et al.* only investigated the phenotypic variant chronic lymphocytic leukemia. When we performed analyses separating chronic lymphocytic leukemia from other NHL types, we found no substantial difference and therefore reported pooled results. For lung, colon, and rectal cancer, our results are also consistent with previous findings of increased MRRs in patients with a history of SCC.[19, 21, 22, 24] In both colon and rectal cancer, only Kahn *et al.* found no increase in the mortality rate. This discrepancy may be explained by the fact that they did not differentiate between NMSC subtypes, since Hjalgrim *et al.* and Nugent *et al.* showed that survival after diagnosis with these cancers was better for BCC than SCC.

In our study, we included 4-month survivors since we wanted to examine the effect of initial cancer therapies. If patients were dying at a high rate in the first months after diagnosis this could explain why our estimates were lower than in the previous studies. However, of the 130 patients that were censored in the 4-month period after diagnosis, 128 had died and only 2 of them (one lung and one rectal cancer patient) had a history of SCC.

Conclusion and perspective

Previous studies have found an increased risk of cancer in SCC patients.[17-20] Other studies have extended this to also include an increased mortality of cancer, but they did not take comorbidities and treatment into account. Our results support this previous finding and suggest that differences in comorbidity and treatment are unlikely to have added substantial confounding to their results.

We suggest that the increased risk and mortality of cancer in SCC patients results from an underlying immunodeficiency, but laboratory studies are needed to clarify the mechanism. In this sense it may be interesting to examine the long-term effects of UVR on the immune system and whether dissimilarities in *e.g.* the antigenic potential of the subsequent cancer could explain the observed differences between cancers.

In Denmark, a "National Cancer Plan" with the aim of optimizing diagnosis and survival of cancer has existed since the year 2000.[58] It has been updated three times with the latest update in 2010.[59] The current plan includes recommendations for screening, diagnostic schemes in patients with occult cancer, subsequent treatments, and follow-up.[58, 59] The increased risk and mortality of cancer in SCC patients suggests that these patients may benefit from additional and more intensive screening. However, the potential efficiency remains to be investigated before introducing such guidelines. At the moment, we therefore advise adherence to the existing recommendations.

Summary

Non-melanoma skin cancer (NMSC) is the most common cancer among Caucasians and the incidence has been increasing worldwide over recent decades. This report concerns squamous cell carcinoma (SCC), which is the second most frequent NMSC subtype. Although the prognosis of SCC is good, it is associated with high morbidity and an increased risk of developing both subsequent NMSC and other malignancies. Furthermore, it has been suggested that SCC is associated with an increased mortality of subsequent cancer, but none of the previous studies included information on important factors such as cancer treatments and comorbidity. Therefore, taking these factors into account, while focusing on the most common types of cancers, we conducted a nationwide population-based cohort study to evaluate whether a history of SCC has prognostic impact in patients with a subsequent diagnosis of one of the following index cancers: non-Hodgkin's lymphoma (NHL), or cancer of the lung, colon, rectum, breast, or prostate.

We based the study on various Danish national medical databases and linked them at the individual level using the unique central personal identification number assigned to every Danish citizen at birth and to residents at immigration. To include information on initial cancer therapies, follow-up started four months after index cancer diagnosis, and continued until death, emigration, diagnosis of SCC in patients without that history at diagnosis of index cancer, end of follow-up (31 December 2008), or a maximum of 10 years, whichever came first. Using Cox proportional hazards regression, we calculated all-cause and cancer-specific mortality rate ratios (MRRs) with 95% confidence intervals (CIs), adjusting for age, gender, comorbidity, index cancer treatments, and calendar period at index cancer diagnosis.

From 1982 through 2003, we identified 745 index cancer patients with and 79,143 without previous SCC. Overall, previous SCC was associated with an increased mortality of cancer (MRR 1.14, 95% CI: 1.05, 1.24). When examining index cancers separately, increased MRRs were found for cancer of the lung (MRR 1.24, 95% CI: 1.06, 1.45), colon (MRR 1.18, 95% CI: 0.96, 1.46), rectum (MRR 1.34, 95% CI: 1.04, 1.73), breast (MRR 1.09, 95% CI: 0.83, 1.44), and NHL (MRR 1.11, 95% CI: 0.82, 1.49), but not for prostate cancer (MRR 0.99, 95% CI: 0.83, 1.18). Adjustments for comorbidity and treatment had no substantial effect on the results.

In conclusion, our results suggest that previous SCC is associated with poor survival for some cancers even after adjustment for comorbidity and cancer treatments. This finding stresses the importance of adherence to existing screening recommendations and diagnostic schemes, especially in SCC patients.

Dansk resumé

Almindelig hudkræft udgør den hyppigste kræftform i Danmark. Den inddeles i flere undertyper, hvor vores projekt omhandler den anden hyppigste form (spinocellulær hudkræft). Antallet af nye tilfælde af spinocellulær hudkræft per år er højt og stadig stigende over hele verden. Selvom prognosen normalt er god, er sygdommen forbundet med høj sygelighed (morbiditet) og en øget risiko for at få en ny hudkræft samt andre typer af kræft. Ydermere har enkelte studier fundet at kræftpatienter med tidligere spinocellulær hudkræft har en øget dødelighed i forhold til kræftpatienter uden tidligere spinocellulær hudkræft. Disse studier har dog ikke taget højde for, om dette kan skyldes forskelle i hvilken behandling patienterne har modtaget eller tilstedeværelse af anden sygdom (komorbiditet). Vi gennemførte derfor en landsdækkende undersøgelse af om tidligere spinocellulær hudkræft er en markør for dårligere overlevelse i patienter med lungekræft, tyktarmskræft, endetarmskræft, brystkræft, blærehalskirtelkræft (prostatakræft) eller non-Hodgkin lymfom, mens vi tog højde for disse faktorer.

Undersøgelsen er gennemført ved at sammenkøre data fra cancerregistret, landpatientregistret, CPR-registeret og dødsårsagsregistret, der registrerer hhv. nye kræfttilfælde, diagnoser, ændringer i vital status (f.eks. dødsfald og migration), og årsager til død. Fra 1982 til og med 2003 inkluderede vi 745 kræftpatienter med og 79.143 kræftpatienter uden tidligere spinocellulær hudkræft. De blev fulgt op indtil død, emigration, spinocellulær hudkræft diagnose i patienter uden tidligere diagnose heraf, 31. december 2008, eller 10 års opfølgning. Vi beregnede overlevelsen hos patienter med tidligere spinocellulær hudkræft sammenlignet med kræftpatienter uden tidligere spinocellulær hudkræft. I beregningerne tog vi højde for alder, køn, komorbiditet, kræftbehandling og kalenderår for kræftdiagnosen.

Overordnet fandt vi at tidligere spinocellulær hudkræft var associeret med 14% dårligere overlevelse af kræft. Når vi undersøgte hver enkelt kræfttype for sig fandt vi en 9-24% dårligere overlevelse for alle typer undtaget blærehalskirtelkræft.

Vi kan ikke udelukke at det er sket en vis misklassification af hvorvidt patienter tidligere har haft spinocellulær hudkræft og at rygning og andre livsstilsfaktorer forklarer en del af den øgede risiko. Disse fejlkilder kan dog ikke forklare hele forskellen.

Vores resultater indikerer at overlevelsen efter nogen typer kræft afhænger af om man tidligere har haft spinocellulær hudkræft, selv efter at man taget højde for forskelle i komorbiditet og kræftbehandling. Det er derfor særlig vigtigt at følge de nuværende retningslinjer for tidlig diagnosticering og behandling af kræft hos patienter der tidligere har haft spinocellulær hudkræft.

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Appendix

Appendix: International Classification of Diseases (ICD) codes used in the study

SCC and index cancers	
Squamous Cell Carcinoma	ICD-10: C44; Morphological code: 80513, 80523, 80703, 80713, 80743, 80753, 80763, 80943, 80953
Lung cancer	ICD-10: C34
Colon cancer	ICD-10: C18
Rectal cancer	ICD-10: C20
Breast cancer	ICD-10: C50
Prostate cancer	ICD-10: C61
Non-Hodgkin's lymphoma (including chronic lymphocytic leukemia)	ICD-10: C82-C85, C88, C90, C91, C96
HIV and solid organ transplantation	
HIV infection	ICD-8: 079.83, Y40.49, Y41.49; ICD-10: B20-B24, F02.4
Solid organ transplantation	ICD-8: 997.70, 997.79, Y95.09, Y95.89; ICD-10: T86.1-4, 94.0-4, Z94.8A; Danish classification of surgical procedures: 322.09, 322.29, 322.50, 356.09, 472.70, 472.79, 488.40, 488.49, 574.80, 574.90; NCSP classification of surgical procedures: FQ, GDG, JLE, JJC, KAS
Cause of death with ICD codes, grouped as defined by the National Board of Health into 14 categories	
1. Tuberculosis, incl. sequelae	ICD-8: 010-019; ICD-10: A15-A19, B90
2. Infectious diseases excl. tuberculosis	ICD-8: 000-009, 020-136; ICD-10: A00-A09, A20-A99, B00-B89, B91-B99
3. Malignant tumors	ICD-8: 140-209; ICD-10: C00-D09
4. Dementia and stroke etc.	ICD-8: 290.09, 430-438, 440, 441, 442, 794; ICD-10: F03.9, I60-I72, R54
5. Heart disease	ICD-8: 390-398, 400-404, 410-414, 420-429; ICD-10: I00-I25, I27, I30-I52
6. Diseases of the respiratory tract	ICD-8: 460-474, 480-486, 490-493, 500-519; ICD-10: J00-J99
7. Diseases of the digestive organs	ICD-8: 520-577; ICD-10: K00-K93
8. Diseases of the urinary and reproductive organs	ICD-8: 580-629; ICD-10: N00-N99
9. Congenital Malformations and Chromosomal Anomalies	ICD-8: 740-759; ICD-10: Q00-Q99
10. Certain Conditions Originating in Perinatal Period	ICD-8: 760-779; ICD-10: P00-P96
11. Suicide	ICD-8: E950-959; ICD-10: X60-X84, Y87.0
12. Homicide	ICD-8: E960-E999; ICD-10: X85-Y09, Y87.1
13. Accidents etc.	ICD-8: E800-E807, E810-E823, E825-E949; ICD-10: V01-X59, Y10-Y86, Y87.2, Y88-Y89
14. All other causes of death	Remaining numbers
ICD codes for autoimmune diseases	
Hematological system	
Autoimmune hemolytic anemia	ICD-8: 283.90; ICD-10: D59.0, D59.1
Ideopatic thrombocytopenic purpura	ICD-8: 287.10; ICD-10: D69.3
Endocrine system	
Graves' disease	ICD-8: 242.00, 242.01, 242.08, 242.09; ICD-10: E05.0
Autoimmune thyroditis	ICD-8: 244.01, 245.03; ICD-10: E06.3
Addison´s disease	ICD-8: 255.10; ICD-10: E27.1
Diabetes type I	ICD-8: 249; ICD-10: E10
Central nervous/ neuromuscular system	
Multiple sclerosis	ICD-8: 340; ICD-10: G35

Myasthenia gravis	ICD-8: 733.09; ICD-10: G70.0
Gastrointestinal/hepatobiliary system	
Pernicious anemia	ICD-8: 281.00, 281.01, 281.08, 281.09; ICD-10: D51.0
Coelic disease	ICD-8: 269.00; ICD-10: K90.0
Crohn´s disease	ICD-8: 563.01, 563.02, 563.09; ICD-10: K50, M07.4
Ulcerative colitis	ICD-8: 563.19; ICD-10: K51, M07.5
Primary biliary cirrhosis	ICD-8: 571.90; ICD-10: K74.3
Skin	
Atopic dermatitis	ICD-8: 691.00; ICD-10: L20
Pemphigus/pemphigoid	ICD-8: 694.00-694.03, 694.05; ICD-10: L10.0, L10.1, L10.2, L10.4, L12.0
Dermatitis herpetiformis	ICD-8: 693.08, 693.09; ICD-10: L13.0
Psoriasis	ICD-8: 696.09, 696.10, 696.19; ICD-10: L40, M07.0-M07.3
Vitiligo	ICD-8: 709.01; ICD-10: L80
Connective tissue diseases	
Rheumatoid arthritis	ICD-8: 712.19, 712.29, 712.39, 712.59; ICD-10: M05, M06, G73.7D, I32.8A, I39.8E, I41.8A, I52.8A
Juvenile rheumatoid arthritis	ICD-8: 712.09; ICD-10: M08
Ankylosing spondylitis	ICD-8: 712.49; ICD-10: M45, H221B
Polymyositis/dermatomyositis	ICD-8: 716.09, 716.19; ICD-10: M33
Systemic- and subacute cutaneous lupus erythematosus	ICD-8: 734.19; ICD-10: M32, G05.8A, G73.7C, I32.8B, I39.8C, L93.1, L93.2, N08.5A, N16.4B
Systemic scleroderma	ICD-8: 734.00-734.09; ICD-10: M34.0-34.9
Mixed connective tissue disease	ICD-8: 734.91; ICD-10: M35.1
Sjögren´s syndrome	ICD-8: 734.90; ICD-10: M35.0, G73.7A, N16.4A
Sarcoidosis	ICD-8: 135.99; ICD-10: D86, G53.2, H22.1A, I41.8B, K77.8B, M63.3
Vasculitis syndromes including polymyalgia rheumatica	ICD-8: 287.09, 446.09-446.99; ICD-10: D69.0B, I77.6, L95, M30-M31, M35.3, M35.6, M79.3, N08.5B-N08.5E
Pulmonary system	
Idiopathic fibrosing alveolitis (pulmonary fibrosis)	ICD-8: 517.01; ICD-10: J841A, J841B, J841C
Ocular diseases	
Iridocyclitis	ICD-8: 364; ICD-10: H200, H201
Any autoimmune disease	If any of the codes listed above

Manuscript

Title: Mortality in cancer patients with a history of squamous cell carcinoma – a nationwide population-based cohort study

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ABSTRACT

Introduction: Squamous cell carcinoma (SCC) is associated with underlying immunosuppression, so it may be a prognostic marker in patients with subsequent cancer. We therefore conducted a nationwide population-based Danish cohort study to evaluate whether a history of SCC has prognostic impact in patients with one of the following index cancers: non-Hodgkin's lymphoma (NHL), or cancer of the lung, colon, rectum, breast, or prostate.

Methods: We used Danish medical databases, which cover the entire Danish population of 5.6 million inhabitants and linked them using the unique personal identification number assigned to all Danish residents. From 1982 through 2003, we identified 745 index cancer patients with and 79,143 without previous SCC. Using Cox proportional hazards regression, we calculated adjusted mortality rate ratios (MRRs) with 95% confidence intervals (CIs).

Results: Overall, previous SCC was associated with an increased mortality of cancer (MRR 1.13, 95% CI: 1.04–1.23). When examining index cancers separately, increased MRRs were found for cancer of the lung (MRR 1.23, 95% CI: 1.05–1.43), colon (MRR 1.13, 95% CI: 0.92–1.40), rectum (MRR 1.29, 95% CI: 1.00–1.67), breast (MRR 1.09, 95% CI: 0.82–1.43), and NHL (MRR 1.09, 95% CI: 0.81–1.47), but not for prostate cancer (MRR 0.99, 95% CI: 0.83–1.18).

Conclusions: Our results suggest that previous SCC is associated with poor prognosis of some cancers. This finding stresses the importance of adherence to the existing recommendations of screening, diagnosis, and treatment of cancer in patients with a history of SCC.

Keywords: cohort studies; epidemiology; mortality; neoplasm; registries; second primary neoplasm; skin neoplasm; squamous cell carcinoma

Introduction

Non-melanoma skin cancer (NMSC)—basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) [1]—is associated with an increased risk of developing both subsequent NMSC [2] and other malignancies compared with the general population [3-5]. Common risk factors have been proposed as the cause, for example, ultraviolet radiation (UVR) and immune incompetence [6,7]. In particular, SCC is known to be associated with immunosuppression [6,8,9], but whether it is a reliable marker for reduced immune competence that could explain these findings is unknown. Overall, five studies have found higher mortality rates in cancer patients with previous SCC [4,10,11], which also could be explained by reduced immune competence. None of the studies, however, included information on important factors such as cancer treatments and comorbidity. Therefore, taking these factors into account, while focusing on the most common types of cancers, we conducted a nationwide population-based Danish cohort study to examine whether a history of SCC has prognostic impact in patients with a subsequent diagnosis of one of the following index cancers: non-Hodgkin's lymphoma (NHL), or cancer of the lung, colon, rectum, breast, or prostate.

Materials & methods

The current study was conducted using Danish medical databases, which cover the entire Danish population of 5.6 million inhabitants [12]. Accurate and unambiguous linkage of all registries was possible using the unique personal identification number assigned to all Danish residents [12].

Study cohort

From the Danish Cancer Registry (DCR), we identified all patients aged 20 to 99 years with a first diagnosis of an index cancer from 1982 through 2003 occurring in the month after a SCC diagnosis or

later. The DCR contains records of all incident malignant neoplasms in Denmark since 1943 and provides details on morphology, histology, stage of cancer at the time of diagnosis, and initial cancer therapies within four months of diagnosis [13]. All diagnostic codes used in this study are provided in the Supplementary eTable 1.

Given abundant data in the DCR, in combination with the fact that our focus was mortality following the most common cancers in Denmark, we decided that for each selected cancer patient with a history of SCC, we would randomly choose 100 patients with the same index cancer but without preceding SCC.

Initially, we aimed to include human immunodeficiency virus (HIV) diagnosis and previous solid organ transplantation as a measure of immune function, but due to a small numbers of patients in these categories, we excluded all patients with HIV (n=4) or previous solid organ transplantation (n=45). Due to a small numbers of patients with a history of SCC in age groups 20-29 years (n=0), 30-39 years (n=1) and 40-49 years (n=3), we chose not to include these age groups in the analysis.

Mortality data

We identified all-cause death using the Danish Civil Registration System (established on April 2, 1968), which is updated daily and records all changes in vital status, date of death, and migration [12]. We identified cancer-specific death using the Danish Registry of Causes of Death, which contains information on all deaths in Denmark since 1943 [14]. We used the cause of death reported on the death certificate grouped into 14 categories as defined by the National Board of Health [15]. Each death certificate includes one underlying, and up to three immediate causes of death [14]. If any of these causes were a malignancy, we used that as the cause of death.

Comorbidity

We obtained information on comorbid diseases from The Danish National Patient Registry, which provides information about all inpatient admissions to somatic hospitals since 1977, and all outpatient and emergency admissions since 1995 [16]. We categorized the level of comorbidity by using the Charlson Comorbidity Index (CCI) [17], an extensively studied and validated instrument used to predict risk of death from comorbid diseases [17,18]. We computed the CCI score for each study subject based on the complete hospital discharge history for at least 5 years before index cancer diagnosis, and grouped it into three levels: Low=0, medium=1–2, and high>3. In addition, we included a list of diseases more strongly related to immunosuppression, namely autoimmune diseases, as a proxy measure of immune function.

Statistical analysis

To include information on initial cancer therapies, follow-up started four months after index cancer diagnosis, and continued until death, emigration, diagnosis of SCC in patients without that history at diagnosis of the index cancer, end of follow-up (31 December 2008), or a maximum of 10 years, whichever came first. 130 patients who had died or were censored by start of follow-up were not included in the analysis.

Initially, we computed the frequency and proportion of covariates, number of deaths and amount of accumulated person-time within index cancer cohorts, stratified by history of SCC. Then, we calculated crude mortality rate ratios (MRRs) with 95% confidence intervals (CIs) associating previous SCC with mortality.

We used Cox proportional hazard regression to estimate MRRs with 95% CIs for index cancer patients with a history of SCC compared with index cancer patients without such history adjusting for

age group (50-69, 70-79, 80-89, 90-99 years), a variable that calculated the midpoint of the age group divided by exact age for each individual, gender, CCI (low, medium, high), calendar period (1982–1986, 1987–1991, 1992–1996, 1997–2001, 2002–2003), history of autoimmune disease (yes/no), stage (localized, regional, distant, unknown/missing), and the following index cancer treatments: no/symptomatic treatment, chemotherapy, radiation therapy, hormone therapy, operation, and other/missing treatment. To examine the presence of effect modification, we stratified the model on age groups, gender, CCI, and history of autoimmune disease. We also stratified mortality rates on time between SCC and index cancer diagnoses. Next, we fitted a reduced model without adjustment for stage and treatment since we hypothesized that they may be on the causal pathway linking SCC to poor prognosis. That is, decreased immune surveillance may cause faster progression of the cancers and thereby more advanced stage at diagnosis, which in turn affects the choice of treatment. In a subanalysis, we found no substantial difference between the phenotypic variant chronic lymphocytic leukemia and other NHL types and therefore report the pooled results. All analyses were performed for both all-cause and cancer-specific death within each index cancer and overall. 476 persons, who were registered as dead in the CRS, but not in the Danish Registry of Causes of Death, were censored at the date of death in analysis for death from cancer. They did not differ from the total population with regard to exposure. Finally, we assessed the assumption of proportional hazards by graphical examination of log-log plots against log-time and found it not to be violated.

After 2003, information on cancer treatments was not available. In a subanalysis, we excluded treatment from the model, which allowed us to increase the enrollment period from 1982 through 2008, and thereby, include more patients. Lung and breast cancer was left out from this analysis, since their results were affected by adjustment for cancer treatment.

If SCC is diagnosed shortly after an index cancer it could still be a marker of poor prognosis, causing us to underestimate the effect when including such patients in the comparison group. We therefore repeated our analysis after excluding patients receiving an SCC diagnosis within two years after index cancer diagnosis. This exclusion did not change the estimates.

All analyses were performed using STATA® software (version 11.0, STATA, College Station, TX). The study was approved by the Danish Data Protection Agency.

Results

Patient characteristics

We included 745 index cancer patients with and 79,143 without a history of SCC. Patients with previous SCC were older at index cancer diagnosis, were more frequently men, had their index cancer diagnosis in a more recent calendar period, and had higher comorbidity (Table 1). Furthermore SCC patients had more frequently missing stage and treatment information, more often received no or symptomatic treatment (except in breast cancer) and had more frequently a history of any autoimmune disease (Supplementary eTable 2).

Mortality

We observed shorter survival time among those with a history of SCC within all index cancer groups, with an overall median survival time of 1.93 years (lower quartile 0.58 years; upper quartile 5.09 years) in SCC patients and 2.57 years (lower quartile 0.74 years; upper quartile 6.54 years) in patients without SCC (Supplementary eTable 2). The most frequent cause of death was malignancy. We were not able to distinguish between NMSC subtypes for cause of death, but a total of 22 persons died of NMSC (2.95% of deaths) among the exposed and 31 (0.04% of deaths) among the unexposed patients.

Overall, a history of SCC was associated with an increased relative rate of death from cancer (MRR 1.13, 95% CI: 1.04–1.23) (Table 2). When examining index cancers separately, increased MRRs were found for cancer of the lung (MRR 1.23, 95% CI: 1.05–1.43), colon (MRR 1.13, 95% CI: 0.92–1.40), rectum (MRR 1.29, 95% CI: 1.00–1.67), breast (MRR 1.09, 95% CI: 0.82–1.43), and NHL (MRR 1.09, 95% CI: 0.81–1.47). There was no increased rate of dying of prostate cancer (MRR 0.99, 95% CI: 0.83–1.18). The stratified analysis revealed no effect modification (data not shown).

Impact of prognostic factors

After including all other covariates, adding comorbidity to the model resulted in a 7% attenuation of the MRR for NHL, but had no effect in the remaining cancers. Adjusting for stage did not affect the results, while adjusting for cancer treatment had an impact in lung and breast cancer in the sense that it raised their MRRs by approximately 7%.

Increasing the enrollment period to 2008 resulted in no substantial change for prostate (MRR 1.03, 95% CI: 0.88–1.21) and colon cancer (MRR 1.10, 95% CI: 0.90–1.33), while an increase was observed for rectal cancer (MRR 1.43, 95% CI: 1.13–1.81) and NHL (MRR 1.23, (95% CI: 0.96–1.57).

Discussion

We found that a history of SCC was associated with a moderately increased mortality rate following a diagnosis of cancer of the lung, colon, rectum, breast, and NHL, but not in survivors of prostate cancer. The present study is the first to examine this association taking into account comorbidity and index cancer treatments. Adjustment for these factors had no substantial effect on our results, so it is unlikely that they have introduced major confounding in previous studies.

In agreement with the extant literature [4,10,19,20,11], we find an overall increased mortality rate in cancer patients with a history of SCC. When examining index cancer types individually, there are, however, some inconsistencies with previous studies. Askling *et al.*, Kahn *et al.*, and Nugent *et al.* included prostate and breast cancer in their studies. All three studies found a 19 to 45% increased mortality rate among breast cancer patients with a history of SCC. In comparison, we found a 9% increase. In contrast to Askling *et al.* and Kahn *et al.*, we found no increased rate of death from prostate cancer. For the remaining index cancers, the finding of a poorer prognosis in patients with previous SCC is consistent across studies [4,10,11,19,20]. In both colon and rectal cancer, only Kahn *et al.* found no increase in the mortality rate. This difference may be explained by the fact that they did not differentiate between NMSC subtypes, since Hjalgrim *et al.* and Nugent *et al.* showed that MRRs for these cancers were lower for BCC than SCC patients.

An association between a history of SCC and a poor prognosis may be explained by an underlying immunodeficiency. Cumulative UVR exposure, the major risk factor of SCC [1], is especially interesting since UVR induces cellular immune incompetence [6]. This reduced immune function may be observed both locally and systemically and it is more pronounced in patients with previous skin cancer than in the general population [6,21]. We therefore hypothesize that SCC is a marker of underlying immunosuppression that compromises the patient's normal immune surveillance against nascent tumor cells resulting in poor prognosis of subsequent cancer. NHL is interesting from this immunologic perspective, given its strong association with immune function. Hence, we would have expected a greater increase compared with the other cancers that are not as strongly related to immune function. However, the imprecision of our estimates, especially for NHL, limit us from concluding on any substantial differences between cancers.

Our study has several limitations. Even though the Danish Cancer Registry is close to complete for most malignancies [13], NMSC registration is probably underreported [5,22] due to the high incidence of NMSCs burdening the systems and the high cure rate that may cause clinicians to consider it trivial, especially in patients with comorbidity [23]. We do not, however, find it likely that mortality of a malignancy occurring later in time would affect misclassification of SCC.

Misclassification of cause of death may be possible. The Danish Registry of Causes of Death has varying validity for different causes of death, although it is almost complete for cancer deaths [14,24,25]. The major problem with the registry is that the sequence of events may not be accurate [25]. To avoid this problem, we considered cause of death to be cancer if any cause on the death certificate was a malignancy. Moreover, we repeated all analyses for all-cause death by using the civil registration system, which is virtually complete [12]. This change in outcome slightly attenuated the results, but they were not substantially different from the cancer-specific MRRs.

Surveillance bias might have affected our results if preceding SCC is associated with increased medical surveillance leading to earlier diagnosis, and hence, better prognosis. This bias would have worked against the direction of the observed association, so it cannot explain the results. In addition, a Danish study of NMSC and risk of subsequent cancer found no evidence of more intensive surveillance for internal malignancies [5], which is in accordance with Danish guidelines on follow-up in SCC patients [26]. Moreover, we found no substantial difference between mortality rates stratified on time between SCC and index cancer diagnoses.

In conclusion, the present study is the first to examine mortality in cancer patients with previous SCC, taking comorbidity and cancer treatments into account. Previous studies have found an increased risk of cancer in SCC patients [3-5] and our study extends this to also include an increased mortality of some types of cancer. Given the increasing SCC incidence [1], these results stress the importance of

adherence to the existing recommendations of screening, diagnosis, and treatment of cancer in patients with a history of SCC.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

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Tables

Table 1. Selected characteristics of persons diagnosed with an index cancer (cancer of the lung, colon, rectum, breast, prostate, or non-Hodgkin's lymphoma (NHL)) in Denmark 1982-2003, by history of squamous cell carcinoma (SCC)

Characteristics	Lung cancer		Colon cancer		Rectal cancer	
	+ SCC (%)	– SCC (%)	+ SCC (%)	– SCC (%)	+ SCC (%)	– SCC (%)
Total	175	18,662	138	14,647	77	7,089
Gender						
Men	140 (80)	11,673 (63)	87 (63)	6,592 (45)	60 (78)	4,086 (58)
Women	35 (20)	6,989 (37)	51 (37)	8,055 (55)	17 (22)	3,003 (42)
Age group (years)[a]						
50-69	49 (28)	11,471 (61)	23 (17)	5,968 (41)	15 (19)	3,383 (48)
70-79	82 (47)	5,895 (32)	48 (35)	5,479 (37)	34 (44)	2,487 (35)
80-89	41 (23)	1,241 (6.7)	59 (43)	2,958 (20)	22 (29)	1,107 (16)
90-99	3 (1.7)	55 (0.3)	8 (5.8)	242 (1.7)	6 (7.8)	112 (1.6)
Calendar period[b]						
1982-1986	19 (11)	3,798 (20)	12 (8.7)	3,023 (21)	11 (14)	1,565 (22)
1987-1991	25 (14)	3,866 (21)	26 (19)	3,219 (22)	15 (19)	1,557 (22)
1992-1996	47 (27)	4,101 (22)	35 (25)	3,324 (23)	22 (29)	1,578 (22)
1997-2001	66 (38)	4,832 (26)	49 (36)	3,549 (24)	17 (22)	1,683 (24)
2002-2003	18 (10)	2,065 (11)	16 (12)	1,532 (10)	12 (16)	706 (10)
Comorbidity level[c]						
Low	81 (46)	12,081 (65)	81 (59)	10,806 (74)	54 (70)	5,477 (77)
Moderate	69 (39)	5,306 (28)	47 (34)	3,221 (22)	18 (23)	1,365 (19)
High	25 (14)	1,275 (6.8)	10 (7.3)	620 (4.2)	5 (6.5)	247 (3.5)

	Breast cancer		Prostate cancer		NHL[d]	
	+ SCC (%)	– SCC (%)	+ SCC (%)	– SCC (%)	+ SCC (%)	– SCC (%)
Total	113	10,418	186	21,364	56	6,963
Gender						
Men	–	–	186 (100)	21,364(100)	46 (82)	3,896 (56)
Women	113 (100)	10,418 (100)	–	–	10 (18)	3,067 (44)
Age group (years)[a]						
50-69	25 (22)	6,298 (60)	18 (9.7)	7,014 (33)	11 (20)	3,253 (47)
70-79	38 (34)	2,569 (25)	83 (45)	9,423 (44)	21 (38)	2,492 (36)
80-89	40 (35)	1,369 (13)	77 (41)	4,61 (22)	20 (36)	1,130 (16)
90-99	10 (8.9)	182 (1.8)	8 (4.3)	308 (1.4)	4 (7.1)	88 (1.3)
Calendar period[b]						
1982-1986	6 (5.3)	1,866 (18)	20 (11)	3,825 (18)	8 (14)	1,261 (18)
1987-1991	18 (16)	2,029 (19)	30 (16)	4,562 (21)	10 (18)	1,392 (20)
1992-1996	28 (25)	2,469 (24)	39 (21)	4,333 (20)	13 (23)	1,659 (24)
1997-2001	44 (39)	2,806 (27)	69 (37)	5,700 (27)	15 (27)	1,876 (27)

2002-2003	17 (15)	1,248 (12)	28 (15)	2,944 (14)	10 (18)	775 (11)
Comorbidity level[c]						
Low	77 (68)	8,406 (81)	106 (57)	14,554 (68)	28 (50)	5,183 (74)
Moderate	29 (26)	1,667 (16)	58 (31)	5,558 (26)	20 (36)	1,517 (22)
High	7 (6.2)	345 (3.3)	22 (12)	1,252 (5.9)	8 (14)	263 (3.8)

[a] Age at index cancer diagnosis

[b] Calendar period of index cancer diagnosis

[c] Three levels of comorbidity were defined based on Charlson index scores of 0 (low), 1-2 (medium), and >2 (high)

[d] Includes the phenotypic variant chronic lymphocytic leukemia

Table 2. Mortality rate ratios for death from cancer, associated with prior squamous cell carcinoma in persons diagnosed with cancer of the lung, colon, rectum, breast, prostate, or non-Hodgkin's lymphoma (NHL) in Denmark 1982-2003

	Unadjusted MRR (95% CI)	Adjusted[a] MRR (95% CI)
Lung cancer	1.27 (1.09–1.48)	1.23 (1.05–1.43)
Colon cancer	1.31 (1.06–1.61)	1.13 (0.92–1.40)
Rectal cancer	1.53 (1.19–1.98)	1.29 (1.00–1.67)
Breast cancer	1.37 (1.05–1.81)	1.09 (0.82–1.43)
Prostate cancer	1.11 (0.93–1.32)	0.97 (0.81–1.15)
NHL[b]	1.46 (1.09–1.96)	1.09 (0.81–1.47)
Overall	1.24 (1.14–1.35)	1.13 (1.04–1.23)

CI: confidence interval

[a] All estimates are adjusted for age group, age group divided by exact age for each individual, gender, Charlson comorbidity index (low, medium, high), calendar period (1982-1986, 1987-1991, 1992-1996, 1997-2001, 2002-2003), a history of any autoimmune disease (yes/no), stage (localized, regional, distant, or unknown/missing), and the following index cancer treatments: no/symptomatic, chemotherapy, radiation therapy, hormone therapy, operation, and other/missing treatment.

[b] Includes the phenotypic variant chronic lymphocytic leukemia

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