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Hip fracture history and risk of nonmelanoma skin cancer: a Danish population-based study

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Background: Vitamin D deficiency is associated with osteoporotic fractures, such as hip fracture. Sun exposure, the natural source of vitamin D, is the main risk factor for basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). In this study, we examined the association between a history of hip fracture and risk of BCC and SCC.

Methods: We conducted a population-based case-controlled study using data on BCC and SCC cases registered in the Danish Cancer Registry from 1990–2005. For each case, we selected five population controls matched by age and gender. We used conditional logistic regression to compute odds ratios (OR) and 95% confidence intervals (CI), while adjusting for chronic diseases and socioeconomic status.

Results: A history of hip fracture was associated with a decreased risk of BCC (OR 0.90, 95% CI 0.85–0.94), which was most pronounced in cases of tumors on the trunk, extremities, or at multiple sites. We found no association for SCC (OR 1.07, 95% CI 0.98–1.17).

Conclusion: Our study showed an inverse association between history of hip fracture and risk of BCC, but not of SCC. Sun exposure, resulting in vitamin D synthesis, may explain the link between the two diseases.

Keywords: hip fracture, vitamin D, sunlight, basal cell carcinoma, squamous cell carcinoma

Introduction

Vitamin D is essential for bone mineralization because of its role in maintaining adequate levels of serum calcium and phosphorus.[1] Vitamin D deficiency precipitates and exacerbates osteoporosis and causes muscle weakness, factors which enhance the risk of fractures.[2–5] In humans, vitamin D is mainly obtained through the skin being exposed to direct sunlight.[6] Sunlight also causes oncogenic mutations in the skin leading to skin cancers, including basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and malignant melanoma.[7] Intermittent high sun exposure is the main risk factor for BCC,[8,9] while risk factors for SCC include cumulative sun exposure.[9–14] Other risk factors include immunosuppressive treatments, cutaneous viral carcinogens, chemical carcinogens, ionizing radiation, phototherapy, and smoking.[9–14] The reaction of the skin to sun exposure also impacts skin cancer risk. Skin that burns easily or tans poorly is also a risk factor.[15–17] Two previous Danish studies have reported different mortality patterns among BCC and SCC patients, suggesting differences in the clinical courses of the two diseases.[18,19]

Few data exist on the link between fractures and nonmelanoma skin cancer. In a large case-controlled study in several European countries (Mediterranean Osteoporosis Study), higher self-reported past sunlight exposure was associated with a lower risk

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of hip fracture.[20,21] In a nested case-controlled study, serum 25(OH)D levels of 220 BCC patients and 220 controls were measured.[22] Blood samples were collected 4–21 years before the development of BCC diagnosis/corresponding date for the controls. The findings suggested that higher prediagnostic serum 25(OH)D levels may be associated with increased risk of subsequent BCC.[22] In contrast, another nested case-controlled study of elderly men (>65 years) showed an inverse association between serum 25(OH)D levels and self-reported nonmelanoma skin cancer.[23] Serum 25(OH)D levels was measured at baseline. Information of a history of nonmelanoma skin cancer was collected at baseline and at a five-year follow-up visit.

A Tasmanian study investigated the association between nonmelanoma skin cancer and risk of hip fracture, using nonmelanoma skin cancer as a biomarker for sun exposure.[24] They reported a 31% lower incidence of prior nonmelanoma skin cancer in a cohort of fracture patients using gender-, age-, and calendar year-specific cancer incidence rates in southern Tasmania as reference.[24] However, the study did not consider important potential confounding factors, such as chronic diseases and socioeconomic status. These are both factors that have importance for nonmelanoma skin cancer risk.[14,25] Therefore, we examined the association between a history of hip fracture and subsequent BCC and SCC in a population-based case-controlled study while accounting for detailed information on chronic diseases and socioeconomic status.

Methods

We conducted this nationwide, population-based, case-control study based on the entire Danish population (5.3 million) using Danish medical registries. All residents of Denmark are registered in the Danish Civil Registration System with a unique civil registration number assigned at birth or upon immigration. Information on changes in vital status, such as emigration and death, are registered in the Civil Registration System and the civil registration number can be used to link data on individuals in different Danish registries.[26]

Nonmelanoma skin cancer cases

We used the Danish Cancer Registry to identify all patients with a diagnosis of BCC or SCC recorded between January 1, 1990 and December 31, 2005. The Danish Cancer Registry contains information on primary cases of cancer on a nationwide basis since 1943, and its data has been shown to be 95% complete with a validity of 98%.[27] The Danish Cancer Registry files include information on cancer type, site, morphology, and cancer history. Tumors are 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 topography and morphology.

We first identified patients with nonmelanoma skin cancer using ICD-10 codes C44.0–C44.9, covering all nonmelanoma skin cancer diagnoses. We then identified BCC patients using the ICD-O-3 morphology codes 80903, 80913, 80923, 80933, 80943, and 80953. We identified SCC patients using ICD-O-3 codes 80513, 80523, 80703 (SCC), 80713, 80743, 80753, and 80763. BCC patients, who were diagnosed with SCC after or on the date of their primary BCC diagnosis, were grouped with SCC patients. We excluded patients younger than 40 years (BCC, n = 2789; SCC, n = 74), because hip fracture in this age group is a rare event and seldom of osteoporotic origin.[28]

Based on ICD-10 codes recorded in the Danish Cancer Registry, we divided BCC and SCC patients into three groups according to tumor location, which is a marker for the amount of body surface exposed to sunlight. Tumors in the head and neck area are regarded as a marker of cumulative sunlight exposure.[29,30] However, the head and neck comprise only a small part of the whole body surface, and exposure of these areas alone to the sun results in limited vitamin D synthesis.[31] In contrast, the trunk and extremities represent a larger body surface area and their exposure to sunlight results in much more vitamin D synthesis.[31] We defined head and neck tumors using ICD-10 codes C44.0–C44.4, tumors on the body (trunk and extremities) using ICD-10 codes C44.5–C44.7, and tumors at multiple sites using ICD-10 code C44.8.

General population controls

Approximately five population controls for each BCC or SCC case were individually matched on age, and gender, based on risk-set sampling.[32] A total of 404,919 population controls were extracted from the Civil Registration System.[33]

History of hip fracture

Data on hip fracture were obtained from the Danish National Patient Registry. In Denmark, the National Health Service provides tax-supported free medical care for all citizens. The Danish National Patient Registry contains data on discharges from all nonpsychiatric hospitals since 1977 and on emergency department and outpatient clinic visits since 1995.

Its records include patients' civil registration number, dates of admission and discharge, and up to 20 discharge diagnoses coded by physicians in accordance with ICD-8 until the end of 1993 and the ICD-10 thereafter. We identified hip fractures using the ICD-8 codes 820.00 (fracture of the neck of femur) and 820.01 (pertrochanteric fracture) and the corresponding ICD-10 codes, ie, S72.0 and S72.1, occurring before the diagnosis date or index date for controls.

Data on chronic diseases

Because a number of chronic diseases may increase the risk of hip fracture and may be associated with nonmelanoma skin cancer, we obtained data from the Danish National Patient Registry on any prior hospital diagnosis since 1977 of a nondiabetic endocrine disorder, diabetes, gastrointestinal disorder, leukemia and lymphoma, connective tissue disease, alcohol abuse, chronic obstructive pulmonary disease, neurological disorders leading to increased risk of falls, dementia, congestive heart failure, cerebrovascular disease, solid cancer, malignant melanoma, and chronic renal disease occurring before the diagnosis date or index date for controls.[14,34] Both inpatient and outpatient diagnoses were included. (For details on ICD codes, see Appendix.)

Data on socioeconomic status

A database maintained by Statistics Denmark since 1980 provides detailed data on socioeconomic status for the entire Danish population.[35] We used four variables to classify socioeconomic status among BCC and SCC patients and their population controls, ie, occupational level, educational attainment, income, and marital status.[36] Occupational level and educational attainment were divided in levels in order to classify socioeconomic status (Table 1).[36] Income-based socioeconomic status was divided into four groups according to quartiles of national average income for a given year. The quartiles were calculated based on both cases and controls of the total population before excluding persons aged less than 40 years. Marital status was categorized as married/cohabiting, divorced/widower, and never married on the diagnosis or index date. Information on marital status and education was obtained at the diagnosis or index date. Occupational group and income variables are based on employment status, and nonmelanoma skin cancer patients tend to be elderly and retired when they are diagnosed. Information on occupational level and income was therefore obtained for the period 10 years before diagnosis/index date to a more accurate picture of overall occupational and income status.[36]

Information on educational level was missing for a great number of people (32% of BCC patients and their population controls, and 53% of SCC patients and their population controls). This is due to the fact that most BCC and SCC patients were over 50 years of age on the date of diagnosis, and because information on educational level is only available from 1980 onwards (ie, the year the database was established in Statistics Denmark).

Statistical analysis

We used conditional logistic regression to compute odds ratios (OR) and 95% confidence interval (CI) for the relation between a history of hip fracture and BCC and SCC, respectively, while adjusting for chronic diseases and socioeconomic status. We conducted analyses both with and without educational attainment, 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 OR according to tumor location (ie, head and neck, trunk/extremities, and multiple sites). Because we used risk-set sampling, the estimated exposure OR in a case-control design is an unbiased estimate of the incidence rate ratio.[37] We repeated the analyses stratified by age and gender, in order to assess the effect of these variables. All statistical analyses were performed using STATA® software (version 11.1). The study was approved by the Danish Registry Board.

Results

Descriptive data

Using the Danish Cancer Registry, we identified 69,506 BCC patients and 11,526 SCC patients who were over the age of 40 years and who were recorded in the registry between January 1, 1990 and December 31, 2005. The median age of BCC patients was 69 (range 40–104) years. A total of 33,297 (48%) of BCC patients had head and neck tumors, 15,362 (22%) had tumors located on the trunk and extremities, and 19,909 (29%) had tumors located at multiple sites. BCC patients with tumors located in the head and neck region were in general older than patients with tumors on the trunk/extremities and at multiple sites (data not shown). BCC patients had a similar prevalence of chronic diseases, but a higher socioeconomic status level than their population controls (Tables 1 and 2). The median age of SCC patients was 78 years (40–106) years. Among SCC patients, 6570 (57%) had tumors in the head and neck region, 2782 (24%) had tumors on the trunk or extremities, and 1963 (17%) had tumors at multiple sites. SCC patients with tumors located

Table 1 Characteristics of BCC and SCC cases and population controls

Variable	Characteristics of cases with BCC and population controls		Characteristics of cases with SCC and population controls	
	Cases (%) n = 69,506	Controls (%) n = 347,316	Cases (%) n = 11,526	Controls (%) n = 57,603
Gender				
Female	32,843 (47)	164,092 (47)	4431 (38)	22,147 (38)
Male	36,663 (53)	183,224 (53)	7095 (62)	35,456 (62)
Hip fracture	1930 (3)	10,914 (3)	658 (6)	3034 (5)
Age, median (range), years	69 (40–104)	69 (40–104)	78 (40–106)	78 (40–106)
≤65	27,881 (40)	139,252 (40)	1900 (16)	9487 (16)
65–80	29,371 (42)	146,801 (42)	4999 (43)	24,987 (43)
80+	12,254 (18)	61,263 (18)	4627 (40)	23,129 (40)
Location				
Head and neck	33,297 (48)	166,348 (48)[a]	6570 (57)	32,832 (57)[a]
Body	15,362 (22)	76,755 (22)[a]	2782 (24)	13,905 (24)[a]
Multiple sites	19,909 (29)	99,489 (29)[a]	1963 (17)	9812 (17)[a]
No registration	938 (1)	4688 (1)[a]	211 (2)	1054 (2)[a]
Socioeconomic status				
Occupational level				
Not in the work force	27,387 (39)	142,384 (41)	6715 (58)	33,462 (58)
Unemployed	2143 (3)	12,248 (4)	239 (2)	1234 (2.0)
Below an executive position	16,933 (24)	88,524 (25)	1611 (14)	7996 (14)
Superior or executive position	18,256 (26)	80,236 (23)	2131 (18)	10,986 (19)
Missing information	4820 (7)	23,924 (7)	830 (7)	4146 (7)
Educational level				
No higher education	19,346 (28)	117,306 (34)	2797 (24)	14,193 (25)
Short-medium academic education (1–4 years)	16,869 (24)	75,690 (22)	1722 (15)	8399 (14)
Long academic education (>4 years)	11,235 (16)	40,634 (12)	925 (8)	4329 (7)
Missing information	22,056 (32)	113,686 (33)	6082 (53)	30,839 (53)
Income				
Lowest quartile	14,091 (23)	81,362 (23)	2497 (22)	13,473 (23)
Second lowest quartile	15,083 (23)	80,844 (23)	2583 (22)	13,439 (23)
Second highest quartile	15,501 (22)	78,954 (23)	2664 (23)	13,220 (23)
Highest quartile	19,606 (28)	77,966 (22)	2905 (25)	13,034 (23)
Missing information	5225 (8)	28,190 (8)	877 (8)	4594 (8)
Marital status				
Divorced/widower	20,521 (30)	107,065 (31)	4048 (35)	20,632 (35)
Never married	4237 (6)	25,115 (7)	654 (6)	3722 (6)
Married/cohabiting	39,722 (57)	187,656 (54)	5369 (47)	25,889 (45)
Missing information	5026 (7)	27,480 (8)	1455 (13)	7517 (13)

Note: [a]Corresponding controls gender-matched and age-matched to the BCC cases with the specific tumor site.
Abbreviations: BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

in the head and neck region were generally older than patients with tumors on the trunk/extremities and at multiple sites (data not shown). SCC patients and their population controls had similar socioeconomic status levels (Table 1). SCC patients had a higher prevalence of chronic diseases compared with their population controls (Table 2).

History of hip fracture and risk of BCC

The overall number of patients with a history of hip fracture was 1930 (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. We found that the prevalence of a history of hip fracture was dependent on tumor location ($P < 0.01$). Stratified by location, the number of patients with a history of hip fracture was 1158 (3.5%) among BCC patients with head and neck tumors and 6044 (3.6%) among their controls, corresponding to an adjusted OR of 0.96 (95% CI 0.89–1.02). Among patients with trunk/extremities tumors and their controls, the numbers were 334 (2.2%) and 2019 (2.6%), respectively, corresponding to an adjusted OR of 0.85 (95% CI 0.75–0.96). Among patients with tumors at multiple sites and among their controls the numbers were 404 (2.0%) and 2684 (2.7%), respectively, corresponding to an adjusted OR

Table 2 A history of selected chronic diseases among BCC and SCC cases and their population controls

Variable	Characteristics of cases with BCC and population controls		Characteristics of cases with SCC and population controls	
	Cases (%) n = 69,506	Controls (%) n = 347,316	Cases (%) n = 11,526	Controls (%) n = 57,760
Nondiabetic endocrine disorders	1091 (2)	5,435 (2)	198 (2)	902 (2)
Diabetes types 1 and 2	2095 (3)	12,666 (4)	561 (5)	2559 (4)
Gastrointestinal disorders	484 (1)	1756 (1)	79 (1)	305 (1)
Leukemia and lymphoma	650 (1)	1613 (–)	310 (3)	338 (1)
Connective tissue diseases	1909 (1)	8261 (2)	473 (4)	1,670 (3)
Alcohol abuse	881 (1)	5905 (2)	175 (2)	815 (1)
Chronic pulmonary diseases	3313 (5)	17,432 (5)	800 (7)	3632 (6)
Neurological disorders with increased risk of fall	3233 (5)	15,901 (5)	766 (7)	3235 (6)
Dementia	539 (1)	3761 (1)	215 (2)	1,156 (2)
Congestive heart failure	2191 (3)	11,706 (3)	812 (7)	3356 (6)
Cerebrovascular diseases	4103 (6)	21,912 (6)	1182 (10)	5708 (10)
Solid cancer except skin cancers	4827 (7)	20,600 (6)	1059 (9)	4427 (8)
Malignant melanoma	696 (1)	1302 (–)	118 (1.0)	244 (0.4)
Chronic renal diseases	1268 (–)	384 (1)	245 (2)	297 (1)

Abbreviations: BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

of 0.77 (95% CI 0.69–0.86, Table 3). 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 a previous hospitalization for hip fracture was 657 (5.7%) among SCC patients and 3047 (5.3%) in the control group (Table 4). The corresponding adjusted OR for SCC was 1.07 (95% CI, 0.98–1.17) among patients with a history of hip fracture. We found that the prevalence of a history of hip fracture was dependent of tumor location ($P < 0.01$). Stratified by location, the number of patients with a history of hip fracture was 422 (6.4%) among SCC patients with head and neck tumors and 1874 (5.7%) among their controls, corresponding to an adjusted OR of 1.11 (95% CI 0.99–1.24). Among patients with trunk/extremities tumors and their controls, the numbers were 142 (5.1%) and 652 (4.7%), respectively, corresponding to an adjusted OR of 1.09 (95% CI 0.90–1.33). Among patients with tumors at multiple sites and among their controls, the numbers were 81 (4.1%) and 440 (4.5%), respectively, corresponding to

Table 3 Odds ratios for BCC among cases with a history of hip fracture

	Previous hip fracture among cases and their controls		OR for BCC	
	Cases n (%)	Controls n (%)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Total	1930 (2.8)	10,914 (3.1)	0.87 (0.83–0.92)	0.90 (0.85–0.94)
Stratified by localization				
Head and neck tumors	1158 (3.5)	6044 (3.6)	0.95 (0.89–1.02)	0.96 (0.90–1.02)
Trunk/extremities	334 (2.2)	2019 (2.6)	0.81 (0.72–0.92)	0.85 (0.75–0.96)
Multiple sites	404 (2)	2684 (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)	3777 (3)	0.85 (0.78–0.93)	0.88 (0.80–0.95)
80+	1175 (10)	6543 (11)	0.88 (0.83–0.94)	0.90 (0.84–0.97)[b]
Stratified by gender				
Male	476 (2)	2846 (2)	0.83 (0.75–0.92)	0.87 (0.79–0.96)
Female	1454 (4)	8068 (4)	0.89 (0.84–0.94)	0.91 (0.86–0.97)

Notes: [a]Adjusted for occupational level, income, marital status, nondiabetic endocrine diseases, diabetes, gastrointestinal disorders, leukemia and lymphoma, connective tissue diseases, alcohol abuse, chronic pulmonary, neurological diseases, dementia, congestive heart diseases, solid cancer (except skin cancer), malignant melanomas, cancer, and chronic renal disease; [b]occupational level was excluded in the adjusted analyses in the 80+ stratum.
Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; OR, odds ratio.

Table 4 Odds ratios for SCC among cases with a history of hip fracture

	Previous hip fracture among cases and their controls		OR for SCC	
	Cases n (%)	Controls n (%)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Total	657 (6)	3047 (5)	1.09 (1.00–1.20)	1.07 (0.98–1.17)
Stratified by localization				
Head and neck tumors	422 (6)	1874 (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	521 (11)	2346 (10)	1.13 (1.02–1.26)	1.14 (1.03–1.27)[b]
Stratified by gender				
Male	222 (3)	1048 (3)	1.07 (0.92–1.24)	1.03 (0.89–1.20)
Female	435 (10)	1999 (9)	1.11 (0.99–1.24)	1.09 (0.98–1.23)

Notes: [a]Adjusted for occupational level, income, marital status, nondiabetic endocrine diseases, diabetes, gastrointestinal disorders, leukemia and lymphoma, connective tissue diseases, alcohol abuse, chronic pulmonary diseases, neurological diseases, dementia, congestive heart diseases, solid cancer (except skin cancer), malignant melanomas, cancer, and chronic renal disease; [b]occupational level was excluded in the adjusted analyses in the 80+ stratum.
Abbreviations: BCC, squamous cell carcinoma; CI, confidence interval; OR, odds ratio.

an OR of 0.94 (95% CI 0.73–1.21), Table 4). Risk estimates stratified by gender were virtually the same.

Discussion

Our results suggest an inverse association between a history of hip fracture and the risk of BCC. This was most pronounced for tumors located on the trunk, extremities, and at multiple sites, which are markers of intermittent high sun exposure to large body surfaces, resulting in more vitamin D synthesis;[31] the larger the body surface area exposed to the sun, the higher the synthesis of vitamin D.[31]

Our results suggest an increased risk of SCC in patients with a history of hip fractures. However, stratified by location, the OR for tumors on the trunk, extremities, and at multiple sites were lower than for head and neck tumors. Factors other than sun exposure, eg, smoking, chronic diseases, and immunosuppression, play a more significant role in the pathogenesis of SCC than of BCC,[10,12–14] 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[3,5,20] and an elevated risk of skin cancer.[7] Our results are consistent with the finding of self-reported high sun exposure being associated with a lower hip fracture risk.[20,21] Our findings are also consistent with the reported higher prediagnostic serum 25(OH)D levels associated with an increased risk of subsequent BCC,[22] and the Tasmanian study reporting a reduced risk of prior nonmelanoma skin cancer in a fracture cohort.[24] However, variables of importance for the risk of hip fracture were not taken into account in this study. Our study extends previous research by addressing the association while accounting for a wide range of covariates, including socioeconomic status and chronic diseases. Using nonmelanoma skin cancer patients as a measure of high sun exposure, the recall bias of self-reporting measures of sunlight exposure is avoided. In addition, we stratified our analyses by tumor location as a marker of sun exposure. Our results are inconsistent with the inverse association between 25(OH)D levels and nonmelanoma skin cancer found in elderly men. However, as the authors of the study suggest, their findings may be due to sun avoidance behaviors after their diagnosis of nonmelanoma skin cancer, because they measured 25(OH)D levels at baseline and recorded a history of skin cancer at baseline or five years after baseline. We investigated the association prior to the diagnosis of skin cancer.

In our study, we lacked information on patterns of sun exposure in patients with BCC and SCC. It is possible that different sun exposure patterns prior to development of BCC and SCC may explain the difference in association between prior hip fracture and risk of BCC and SCC, respectively. Intermittent and regular sun exposure of unprotected skin is the best way to increase vitamin D accumulation,[6] but is also associated with development of BCC.[8]

In contrast, cumulative prolonged sun exposure of unprotected skin associated with development of SCC[10] does 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 previtamin D is dependent on skin pigmentation (ie, the more pigmentation, the lower the amount of previtamin D synthesized per dose of ultraviolet B).[6,38] In addition, vitamin D itself is photolabile and can be broken down by sunlight.[39,40] A limitation of our study is a lack of information on lifestyle confounders, such as smoking, obesity, and physical activity. However, we were able to adjust for chronic pulmonary disease as a proxy measure for smoking.

Earlier findings from Jensen et al support our findings. They reported better survival among BCC patients, showing reduced cause-specific mortality from cardiovascular disease, chronic pulmonary disease, and diabetes mellitus among patients with BCC, the diseases against which vitamin D is suggested to be protective.[18,41] In contrast, Jensen et al found increased mortality among SCC patients compared with the general population, emphasizing differences in the clinical course of BCC and SCC.

A limitation of the study is lack of information regarding medication, which precludes us from adjusting for medication to treat osteoporosis, which may have influenced our results by decreasing fracture risk. Further, we were unable to adjust for immunosuppressive medication increasing the risk of nonmelanoma skin cancer, especially SCC. Selection of cases and controls might have introduced some selection bias in our design. However, a major strength of our study was selection of controls from the general population, providing an unbiased control group.[42] Another limitation is possible under-registration or under-ascertainment of nonmelanoma skin cancer due to the favorable prognosis of nonmelanoma skin cancer.[43] We cannot rule out that this was also influenced by the presence of a history of hip fracture or coexistent chronic disease. If patients with chronic disease have more frequent contact with physicians, this could lead to better ascertainment and registration of nonmelanoma skin cancer in these patients. However, under-ascertainment of nonmelanoma skin cancer in patients with chronic disease could also occur, due to medical attention being focused on the more serious coexistent disease. Both scenarios would introduce bias due to systematic differences in characteristics between those who are selected for the study and those not selected.[44] The first scenario would skew the data on nonmelanoma skin cancer patients having poorer health, resulting in underestimation of the overall effect of a history of hip fracture on nonmelanoma skin cancer risk. The second scenario would skew the data on nonmelanoma skin cancer patients towards those with better health, leading to potential overestimation of the effect.[44] However, the finding of a more pronounced inverse association between a history of hip fractures and risk of BCC in patients with tumors on trunk/extremities or at multiple sites cannot be explained by this possible bias.

An advantage of our study is the use of prospectively collected routine data on discharge diagnoses from the Danish National Patient Registry, thus avoiding recall bias. The Danish National Patient Registry contains data on 99.4% of all discharges and outpatient clinic visits from Danish nonpsychiatric hospitals.[42] Furthermore, we obtained high quality information on socioeconomic status among all nonmelanoma skin cancer cases and their controls from Statistics Denmark, which gathers information on socioeconomic status variables mainly from tax authorities and the Civil Registration System in Denmark, with high validity.

In conclusion, our results indicate that patients with a history of hip fracture have a reduced the risk of BCC, but not of SCC. The correlation between a history of skin cancer and location of tumor suggests that sun exposure, resulting in vitamin D synthesis, may explain the link between the two diseases.

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Disclosure

The authors report no conflicts of interest in this work.

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Appendix

Covariates with corresponding ICD-8 and ICD-10 codes

	ICD-8	ICD-10
Nondiabetic endocrine disorders		
• Adrenal insufficiency	255.10–255.19	E27.1–E27.4
• Cushing's syndrome	258.00–258.19	E24
• Thyrotoxicosis	242	E05
• Hyperparathyroidism	252.00–252.09	E21
Diabetes types 1 and 2	249; 250	E10; E11
Gastrointestinal disorders		
• Celiac disease	269.00	K90.0
• Inflammatory bowel disease	563.01; 563.19; 569.04	K50.1; K50.8; K50.9; K51.0–51.3
Leukemia and lymphoma	204–207; 200–203; 275.59	C91–C95; C81–C85; C88; C90; C96
Connective tissue diseases	712; 716; 734; 446; 135.99	M05; M06; M08; M09; M30; M31; M32; M33; M34; M35; M36; D86
Alcohol abuse	303	F10
Chronic pulmonary diseases	490–493; 515–518	J40–J47; J60–J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Neurological disorders with increased risk of falls	330–333, 340–343, 344, 345, 353–355, 348; (040–044)	G10–G13; G20–G26 G30–G32, G35–G37, G40; G41, G45–G46; G55–G63, G70–G73, G80–G82, (A80–A82)
Dementia	290.09–290.19; 293.09	F00–F03; F05.1
Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2
Cerebrovascular disease	430–438	I60-I69; G45; G46
Solid cancer except skin cancers	140–194 (except 172 and 173)	C00–C75 (except C43 and C44)
Malignant melanoma	172	C43
Chronic renal diseases	792	N18 N19