# Risk of Second Primary Cancer and Death Following a Diagnosis of Nonmelanoma Skin Cancer

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## Abstract

**Cancer-free patients diagnosed with a first primary nonmelanoma skin cancer (NMSC) offer an opportunity for studying the risk of a second primary cancer without the confounding effect of systemic treatment. The objective of the study was to estimate the risk of second primary cancer in people with a history of basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) and the risk of dying in cancer patients with a NMSC history. BCC and SCC cases diagnosed between 1956 and 2000 in Manitoba, Canada were followed-up for second primaries (other than NMSC). Standardized incidence and mortality ratios (SIR and SMR) were calculated. Men [SIR, 1.06; 95% confidence interval (95% CI), 1.02-1.10] and women (SIR, 1.07; 95% CI, 1.02-1.12) with a BCC history as well as men (SIR, 1.15; 95% CI, 1.08-1.22) with a SCC history were at greater risk of a second primary cancer. Overall, the increased risk was observed only in the first 4 years following a NMSC, although it remained increased for specific cancer sites. The risk remained higher in all age groups up to 75 years of age. People with a history of BCC (males: SMR, 1.09; 95% CI, 1.04-1.14; females: SMR, 1.24; 95% CI, 1.16-1.32) or SCC (males: SMR, 1.18; 95% CI, 1.09-1.27; females: SMR, 1.55; 95% CI, 1.35-1.79) had a greater risk of death following their second primaries. Even if NMSC patients are at greater risk of a second cancer, it is not recommended to follow them up beyond the generally accepted periodic examination of the skin.** (Cancer Epidemiol Biomarkers Prev 2005;14(11):2584–90)

## Introduction

Nonmelanoma skin cancer (NMSC) has been the subject of increasing interest because of its high incidence in Caucasian populations (1, 2) and its potential use as an indicator of the risk of developing a second primary cancer (3, 4). Studies that have investigated the latter topic have focused on three different issues (i.e., the risk of developing another NMSC, the risk of developing any cancer, and the risk of death in cancer patients with a history of NMSC).

In a meta-analysis published in 2000, Marcil and Stern (5) estimated that the average proportion of patients developing a subsequent basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) within 3 years was 44% and 18%, respectively. This risk of a subsequent NMSC was strongly associated with the number of previously diagnosed NMSC.

A few studies, largely European, have examined the risk of developing any cancer following a diagnosis of NMSC. Patients with a history of NMSC were reported to have a greater risk of being diagnosed with cutaneous melanoma, non-Hodgkin's lymphoma, leukemia, and cancers of the lung, salivary glands, mouth and throat, lip, and breast (6-8). Increased risk for other cancer sites has also been reported but not as consistently. Men were also found at greater risk of a second primary than women.

Two European (9, 10) studies and one from the United States (11) compared the outcome of cancer patients with and without a history of NMSC. All three investigations reported a significantly increased risk of dying of non-Hodgkin's lymphoma among patients with a NMSC history. Two of the studies that assessed multiple causes of death reported an increased risk of dying from cutaneous melanoma, Hodgkin's lymphoma, leukemia, and cancers of the colon, salivary glands, pharynx, lung, breast, prostate, testis, and bladder (9, 11).

NMSC is most often treated using surgery or local destructive methods. Because systemic therapy is rarely indicated, NMSC provides a unique opportunity for studying the risk of second primary in patients with a history of cancer. Existing studies suggest that the incidence of few types of cancer is increased following a NMSC, whereas the increase of others may be specific to various regions or simply due to chance. The present study examines the incidence of second invasive primaries (other than NMSC) among patients with a history of BCC or SCC, as well as the risk of death in these patients. It is the first North American population-based investigation reporting on the topic.

## Materials and Method

**Population.** The Manitoba Cancer Registry, which is housed at CancerCare Manitoba, was started in 1937 and became population based in 1956. Cancer reporting is mandated by law in Manitoba, and information on all potential new cases must be forwarded to the Manitoba Cancer Registry. Multiple sources of ascertainment of incident cases are used, including physician notifications, pathology and hematology reports, and hospitalization, mortality, and autopsy records. For every case, the Cancer Registry includes information on diagnosis according to the International Classification of Diseases, 9th edition (ICD-9) code (ICD-10 since 2002), date of diagnosis, tumor grade, tumor morphology, date of birth, sex, vital status, and since a few years stage. The Manitoba Vital Statistics

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**Table 1. Age distribution of patients diagnosed with a first primary BCC and SCC**

| Age | BCC | | SCC | |
|---|---|---|---|---|
| | Male (%) | Female (%) | Male (%) | Female (%) |
| 0-29 | 136 (0.9) | 193 (1.4) | 15 (0.3) | 8 (0.3) |
| 30-34 | 200 (1.3) | 266 (2.0) | 18 (0.4) | 15 (0.5) |
| 35-39 | 380 (2.4) | 448 (3.4) | 46 (0.9) | 19 (0.7) |
| 40-44 | 705 (4.5) | 631 (4.7) | 82 (1.60) | 47 (1.6) |
| 45-49 | 985 (6.3) | 773 (5.8) | 131 (2.6) | 54 (1.9) |
| 50-54 | 1,312 (8.4) | 970 (7.3) | 274 (5.5) | 127 (4.4) |
| 55-59 | 1,512 (9.7) | 1,175 (8.8) | 416 (8.4) | 148 (5.2) |
| 60-64 | 1,906 (12.2) | 1,443 (10.8) | 530 (10.7) | 233 (8.1) |
| 65-69 | 2,283 (14.6) | 1,668 (12.5) | 726 (14.6) | 362 (12.7) |
| 70-74 | 2,311 (14.8) | 1,877 (14.0) | 915 (18.4) | 459 (16.0) |
| 75-79 | 1,956 (12.5) | 1,704 (12.7) | 807 (16.2) | 529 (18.5) |
| 80-84 | 1,260 (8.1) | 1,377 (10.3) | 630 (12.7) | 468 (16.4) |
| 85-89 | 640 (4.1) | 845 (6.3) | 383 (7.7) | 391 (13.7) |
| Median age* | 66.5 | 67.4 | 71.2 | 75.6 |
| Age interquartile* | 55.7-74.9 | 55.3-76.6 | 62.6-78.6 | 66.1-81.6 |
| Total NMSC | 15,586 | 13,370 | 4,973 | 2,860 |
| No. second primary † | 2,945 | 1,673 | 994 | 323 |

*These relate to data that has been censored at age 90 and thus cannot be used for comparison with uncensored data.
†BCC and SCC cases that developed a second primary cancer (excluding NMSC).

department provides information on mortality. In examining cases registered from 1991 to 1995, the North American Association of Central Cancer Registries estimated the Manitoba Cancer Registry to be 95% to 98% complete in ascertaining all cancer cases (12). However, this estimation did not include NMSC.

Due to the workload created for the registry by the high incidence of NMSC in Manitoba, when someone is reported with a second NMSC of the same morphology, the ICD code of the first NMSC is changed to 173.8 (neoplasm of contiguous or overlapping sites of skin whose point of origin cannot be determined). Subsequent skin cancers with different morphology are coded individually. Thus, site-specific statistics are not presented.

**Incident and Death Cases.** Individuals whose first reported invasive cancer was a BCC or a SCC (ICD-9 173) diagnosed in Manitoba between January 1, 1956 and December 31, 2000 were identified and followed-up until the diagnosis of a second primary (ICD-9 140-208, excluding 173), 90 years of age, death, or December 31, 2000, whichever occurred first. BCC included ICD-O codes 8090.3 to 8093.3, and SCC included ICD-O codes 8052.3, 8070.3 to 8076.3, and 8084.3. Patients who were diagnosed with a BCC and a SCC were assigned to both groups. Second primaries occurring from 1 day after the NMSC diagnosis were included in the study.

NMSC cases had to survive for at least 1 week after diagnosis to be included in the mortality analysis. Cancers diagnosed at autopsy or through death certificate only were not included. Survival time was censored at the age of 90 to partially control for people with missing death date. Tumor morphology was available for all NSMC.

**Analyses.** Standardized incidence and mortality ratios were used as measures of relative risk. The expected number of cases was calculated by applying the Manitoba cancer site, age (in 5-year age categories), and sex-specific rates to the cancer site, age, and sex-specific person-time accumulated by the people with a first primary NMSC. Standardized mortality ratios were based on death rates from all causes. Rates were compared between people with NMSC and a specific cancer versus people with this same specific cancer but without antedated NMSC. Risk of a second primary cancer or death were determined for various time periods, from the diagnosis of the NMSC (<1, 1-4, and ≥5 years). Confidence intervals were calculated assuming a Poisson distribution (13). Analyses were done using SAS v9.1.

## Results

Overall, 43,275 NMSC cases were recorded between 1956 and 2000 (21.3% squamous, 74.2% basal, and 4.5% other types of NMSC) A total of 28,956 BCC patients (282,814 person-years) and 7,833 SCC patients (61,416 person-years) with no history of invasive cancer were followed-up. Men represented 53.8% of BCC cases and 63.5% of SCC cases, and women represented 46.2% and 36.5%, respectively (Table 1). A second primary cancer was diagnosed in 16% of the BCC cases and 17% of the SCC cases. The average age at diagnosis of a second primary cancer was 74.3 years, whereas people without a history of NMSC developed their first invasive cancer at an average age of 64.4 years. These results only include cancers developing before age 90.

Men diagnosed with a first primary NMSC between 40 and 79 years of age and women diagnosed between the age of 40 and 74 years had an increased risk for a second primary cancer (Fig. 1). After 79 years of age, the risk declined in men, particularly among the very old. For women over 74 years of age, the risk between the two groups was similar. The risk of second primary was 1.42 [95% confidence interval (95% CI), 1.24-1.63] following a BCC and 1.51 (95% CI, 1.08-2.07) following a SCC for men younger than 60 years of age, whereas it was 1.04 (95% CI, 1.0002-1.08) and 1.13 (95% CI, 1.07-1.21), respectively, for men 60 years of age and older. For women, these risks were 1.27 (95% CI, 1.10-1.46) following a BCC and 1.07 (95% CI, 0.59-1.80) following a SCC for those younger than 60 years of age, and 1.05 (95% CI, 0.9997-1.11) and 1.06 (95% CI, 0.95-1.18), respectively, for those 60 years of age and older.

Men with a history of BCC or SCC had an overall higher risk of being diagnosed with a second primary cancer than patients without such history (Table 2). The risk of lip, salivary gland, cutaneous melanoma, non-Hodgkin's lymphoma, and myeloma were increased in patients with a history

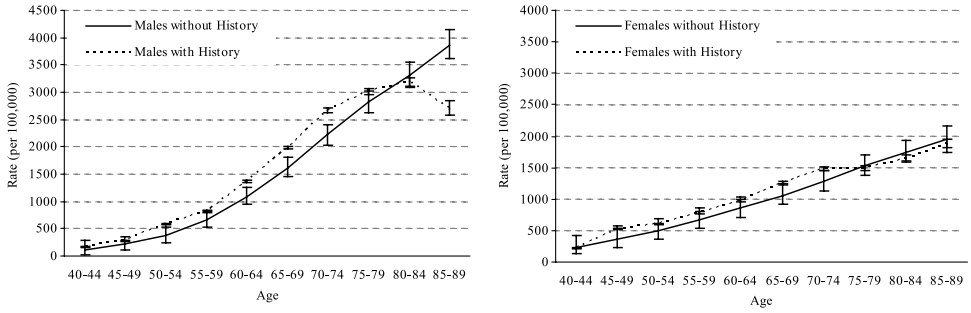


**Figure 1.** Age-specific incidence rates of cancer, other than NMSC, for people with and without a history of NMSC, Manitoba. *Bars*, 95% CI.

**Table 2. Standardized incidence ratios for developing a second primary cancer by type of NMSC, cancer site, and time (y) since diagnosis, males**

| Cancer site* | BCC | | | | | | | | SCC | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <1 | | 1-4 | | ≥5 | | Total | | <1 | | 1-4 | | ≥5 | | Total | |
| | *n* | SIR | *n* | SIR | *n* | SIR | *n* | SIR (95% CI) | *n* | SIR | *n* | SIR | *n* | SIR | *n* | SIR (95% CI) |
| Total excluding NMSC† | 346 | 1.44‡ | 983 | 1.23‡ | 1,616 | 0.93‡ | 2,945 | 1.06 (1.02-1.10) | 133 | 1.39‡ | 391 | 1.34‡ | 470 | 0.98 | 994 | 1.15 (1.08-1.22) |
| Lip | 15 | 2.29‡ | 44 | 2.04‡ | 52 | 1.14 | 111 | 1.50 (1.25-1.81) | 13 | 5.28‡ | 29 | 3.86‡ | 38 | 3.18‡ | 80 | 3.65 (2.93-4.54) |
| Salivary glands | 0 | | 7 | 5.81‡ | 4 | 1.61 | 11 | 2.71 (1.35-4.85) | 1 | 7.70 | 4 | 10.1‡ | 5 | 8.08‡ | 10 | 8.74 (4.19-16.1) |
| Mouth | 1 | 0.60 | 6 | 1.10 | 12 | 1.08 | 19 | 1.04 (0.62-1.62) | 1 | 1.69 | 4 | 2.24 | 2 | 0.72 | 7 | 1.36 (0.55-2.81) |
| Pharynx | 5 | 2.50 | 11 | 1.68 | 18 | 1.37 | 34 | 1.56 (1.08-2.18) | 0 | | 4 | 1.81 | 3 | 0.89 | 7 | 1.11 (0.44-2.28) |
| Esophagus | 1 | 0.36 | 7 | 0.75 | 13 | 0.63‡ | 21 | 0.64 (0.40-0.98) | 0 | | 1 | 0.29 | 3 | 0.54 | 4 | 0.40 (0.11-1.01) |
| Stomach | 11 | 0.77 | 24 | 0.51‡ | 59 | 0.56‡ | 94 | 0.57 (0.46-0.69) | 3 | 0.53 | 16 | 0.92 | 19 | 0.66 | 38 | 0.73 (0.52-1.01) |
| Small intestine | 1 | 1.43 | 1 | 0.43 | 2 | 0.40 | 4 | 0.50 (0.14-1.28) | 0 | | 2 | 2.42 | 0 | | 2 | 0.82 (0.10-2.96) |
| Colon | 16 | 0.74 | 95 | 1.32‡ | 142 | 0.89 | 253 | 1.00 (0.88-1.13) | 9 | 1.03 | 32 | 1.19 | 45 | 1.01 | 86 | 1.07 (0.87-1.33) |
| Rectum | 18 | 1.39 | 36 | 0.84 | 62 | 0.67‡ | 116 | 0.78 (0.65-0.94) | 5 | 0.998 | 14 | 0.91 | 19 | 0.77 | 38 | 0.85 (0.60-1.16) |
| Liver | 4 | 2.30 | 11 | 1.90 | 7 | 0.55 | 22 | 1.09 (0.68-1.64) | 0 | | 4 | 1.86 | 1 | 0.28 | 5 | 0.79 (0.26-1.84) |
| Gall bladder | 1 | 0.50 | 6 | 0.89 | 11 | 0.73 | 18 | 0.76 (0.45-1.20) | 0 | | 2 | 0.79 | 1 | 0.24 | 3 | 0.39 (0.08-1.15) |
| Pancreas | 8 | 1.04 | 19 | 0.74‡ | 42 | 0.75 | 69 | 0.77 (0.61-0.98) | 2 | 0.66 | 14 | 1.50 | 9 | 0.59 | 25 | 0.90 (0.58-1.33) |
| Larynx | 1 | 0.33 | 11 | 1.12 | 22 | 1.11 | 34 | 1.04 (0.72-1.46) | 2 | 1.85‡ | 4 | 1.22 | 5 | 1.01 | 11 | 1.18 (0.59-2.12) |
| Lung | 60 | 1.38‡ | 171 | 1.20‡ | 301 | 1.00 | 532 | 1.09 (1.00-1.19) | 29 | 1.73‡ | 60 | 1.18 | 79 | 0.98 | 168 | 1.13 (0.97-1.32) |
| Connective, soft tissue | 1 | 1.05 | 5 | 1.60 | 9 | 1.36 | 15 | 1.40 (0.78-2.31) | 1 | 2.84 | 3 | 2.79 | 4 | 2.30 | 8 | 2.53 (1.09-4.98) |
| Cutaneous melanoma | 15 | 7.16‡ | 30 | 4.40‡ | 41 | 2.97‡ | 86 | 3.78 (3.06-4.67) | 7 | 8.86‡ | 9 | 3.75‡ | 12 | 3.20‡ | 28 | 4.03 (2.68-5.83) |
| Prostate | 95 | 1.50‡ | 268 | 1.26‡ | 455 | 0.94 | 818 | 1.08 (1.01-1.15) | 28 | 1.06 | 99 | 1.21 | 133 | 0.97 | 260 | 1.06 (0.93-1.19) |
| Bladder | 23 | 1.63‡ | 63 | 1.34‡ | 94 | 0.89 | 180 | 1.08 (0.93-1.25) | 5 | 0.87 | 16 | 0.90 | 25 | 0.84 | 46 | 0.86 (0.63-1.15) |
| Kidney | 8 | 1.24 | 17 | 0.80 | 38 | 0.87 | 63 | 0.88 (0.68-1.13) | 2 | 0.83 | 9 | 1.23 | 9 | 0.79 | 20 | 0.94 (0.58-1.46) |
| Brain, nervous system | 8 | 3.49‡ | 9 | 1.22 | 15 | 1.07 | 32 | 1.35 (0.93-1.91) | 1 | 1.27 | 2 | 0.84 | 2 | 0.58 | 5 | 0.76 (0.25-1.77) |
| Thyroid | 1 | 1.66 | 0 | | 2 | 0.52 | 3 | 0.47 (0.10-1.36) | 0 | | 0 | | 0 | | 0 | |
| Without specification of site | 12 | 1.75 | 29 | 1.27 | 60 | 1.17 | 101 | 1.25 (1.03-1.52) | 5 | 1.80 | 14 | 1.63 | 16 | 1.12 | 35 | 1.37 (0.95-1.90) |
| Non-Hodgkin's lymphoma | 14 | 1.99‡ | 48 | 2.08‡ | 59 | 1.21 | 121 | 1.54 (1.29-1.84) | 7 | 2.60‡ | 23 | 2.80‡ | 16 | 1.22 | 46 | 1.92 (1.40-2.56) |
| Hodgkin's lymphoma | 1 | 1.39 | 3 | 1.28 | 4 | 0.84 | 8 | 1.02 (0.44-2.01) | 2 | 7.78 | 2 | 2.56 | 0 | | 4 | 1.77 (0.48-4.53) |
| Myeloma | 5 | 1.43 | 20 | 1.72‡ | 30 | 1.18 | 55 | 1.36 (1.02-1.77) | 1 | 0.71 | 8 | 1.85 | 12 | 1.71 | 21 | 1.65 (1.02-2.52) |
| Leukemia | 15 | 2.09‡ | 27 | 1.13 | 42 | 0.81 | 84 | 1.02 (0.82-1.26) | 5 | 1.75 | 10 | 1.14 | 8 | 0.56 | 23 | 0.89 (0.56-1.33) |

Abbreviation: SIR, standardized incidence ratio.
*ICD-9 codes for mouth: 141, 143, and 144; pharynx: 145-148; brain and nervous system: 191 and 192; without specification of site: 199; non-Hodgkin's lymphoma: 200 and 202; leukemia: 204-207.
†Total excluding NMSC includes sites not listed.
‡$P < 0.05$.

of BCC or SCC. In addition, the risk of pharyngeal, lung, prostate, and no-specific-site cancers was increased in BCC patients, and the risk of connective/soft tissue cancers was increased in SCC patients. The risk of esophageal, stomach, rectum, and pancreas cancers was reduced in patients with a history of BCC.

For men, the overall risk of a second primary following a BCC or SCC was greater than expected in the first 4 years following a NMSC but not thereafter (Table 2). However, this trend was not observed for all cancer sites. For example, the risk of lip, salivary glands, pharynx, cutaneous melanoma, and no-specific-site cancers as well as non-Hodgkin's lymphoma remained relatively high, although not always significantly, after 4 years of follow-up.

The overall risk of a second primary cancer in females with a BCC was increased, although it was not for those with a SCC history (Table 3). The risk of lip cancer, lung cancer, cutaneous melanoma, and non-Hodgkin's lymphoma was increased in women with a BCC or SCC. In addition, the risk of breast cancer was increased in BCC patients, whereas leukemia was increased in SCC patients. The risk of stomach, gallbladder, pancreas, and cervical cancers was lower in BCC patients, and the risk of myeloma was lower in SCC patients.

Women's risk of a second primary cancer following a diagnosis of BCC was greater than expected for the first 4 years but not thereafter (Table 3). For lip, lung, cutaneous melanoma, breast, and thyroid cancers as well as non-Hodgkin's lymphoma, the risk was greater over all three time periods, although not always significantly.

To have an indication if NMSC patients were under closer medical surveillance than patients being diagnosed with a cancer for the first time, the stage of breast cancer tumors diagnosed between 1995 and 2000 in the two groups was compared. The stage at diagnosis was similar in both groups (women with a NMSC: 149 cases: stage 0, 0.4%; stage I, 61%; stage II, 32%; stage III, 4%; stage IV, 4%; women without a NMSC: 3,325 cases: stage 0, 0; stage I, 63%; stage II, 31%; stage III, 2%; stage IV, 4%; $P = 0.77$). We also examined if women with a NMSC were diagnosed more often with *in situ* cervical cancer than those without a history of NMSC. Based on 29 cases following all forms of NMSC, there was not a significantly different risk (standardized incidence ratio, 0.80; 95% CI, 0.56-1.15).

Males and females with a BCC or SCC history had a greater risk of death following their second primary cancer compared with people who developed the same cancer but as their first primary (Table 4). Males with a history of BCC or SCC were at greater risk of dying following cancers of the mouth/pharynx, esophageal, and kidney/bladder. Males with a BCC history were, in addition, at greater risk of death following colon,

liver/gallbladder/pancreas, lung, and no-specific-site cancers, as well as leukemia. Males with a SCC history also had a greater risk of death following lip cancer, larynx cancer, brain/nervous system cancer, and Hodgkin's lymphoma. Males with a history of BCC were at lower risk of death from prostate cancer.

Females with a history of BCC or SCC were at greater risk of dying following cancers without specification of site. In addition, females with a BCC history had a greater risk of dying following esophageal, colon, liver/gallbladder/pancreas, cervical, uterine, ovarian, and brain/nervous system cancers. Females with a SCC history also had a greater risk of dying following lip, rectal, lung, and breast cancers, as well as non-Hodgkin's lymphoma.

## Discussion

The results of the present study overlap the findings of previous investigations for many cancer sites (Table 5). A greater risk of cutaneous melanoma was the most constant finding reported in patients with a history of NMSC. A greater risk for other cancer sites was also reported but not as consistently. These other sites include lip, salivary glands, mouth and pharynx, lung, and non-Hodgkin's lymphoma. In addition, a greater risk of female breast cancer was often reported following a BCC, as it was for leukemia following a SCC. The decrease in cancer rates in older males with a history of NMSC (Fig. 1) may be partly a consequence of a positive association of NMSC with prostate cancer in conjunction with the recent decrease in the incidence rates of prostate cancer in the oldest age groups in Manitoba.

The overall observed number of second primary (excluding NMSC) was no longer different than expected after 4 years of follow-up. However, for many sites, the risk remained relatively high over time. Three studies that assessed this trend reported a constant risk over time (7, 14, 15), although two of them showed no association (14, 15), and one study reported an increasing trend for men and a decreasing trend for women (6). This limited information makes it difficult, at this point, to generalize on the long-term effect of a history of NMSC on the overall risk of cancer. However, these results support the absence of long-term screening bias for cancer sites that tend not to be identified at the same time as the NMSC. Potential problematic sites include cutaneous melanoma and lip cancer.

**Table 3. Standardized incidence ratios for developing a second primary cancer by type of NMSC, cancer site, and time (y) since diagnosis, females**

| Site* | BCC | | | | | | | | SCC | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <1 | | 1-4 | | ≥5 | | Total | | <1 | | 1-4 | | ≥5 | | Total | |
| | *n* | SIR | *n* | SIR | *n* | SIR | *n* | SIR (95% CI) | *n* | SIR | *n* | SIR | *n* | SIR | *n* | SIR (95% CI) |
| Total excluding NMSC† | 178 | 1.33‡ | 502 | 1.12‡ | 993 | 1.02 | 1,673 | 1.07 (1.02-1.12) | 40 | 1.13 | 122 | 1.11 | 161 | 1.00 | 323 | 1.06 (0.95-1.18) |
| Lip | 3 | 6.27‡ | 7 | 4.31‡ | 19 | 5.18‡ | 29 | 5.03 (3.37-7.22) | 0 | | 3 | 6.30‡ | 5 | 7.03‡ | 8 | 5.97 (2.58-11.8) |
| Salivary glands | 0 | | 1 | 1.33 | 0 | | 1 | 0.39 (0.01-2.15) | 0 | | 0 | | 0 | | 0 | |
| Mouth | 2 | 2.70 | 2 | 0.80 | 8 | 1.49 | 12 | 1.40 (0.72-2.44) | 0 | | 1 | 1.61 | 0 | | 1 | 0.58 (0.01-3.22) |
| Pharynx | 0 | | 3 | 1.32 | 4 | 0.82 | 7 | 0.89 (0.36-1.84) | 0 | | 0 | | 0 | | 0 | |
| Esophagus | 0 | | 4 | 1.06 | 5 | 0.57 | 9 | 0.66 (0.30-1.25) | 0 | | 1 | 0.99 | 2 | 1.30 | 3 | 1.04 (0.22-3.05) |
| Stomach | 8 | 1.43 | 12 | 0.63 | 24 | 0.54‡ | 44 | 0.64 (0.46-0.86) | 3 | 1.83 | 6 | 1.17 | 6 | 0.78 | 15 | 1.04 (0.58-1.71) |
| Small intestine | 0 | | 4 | 2.51 | 5 | 1.38 | 9 | 1.58 (0.72-3.00) | 0 | | 2 | 4.75 | 0 | | 2 | 1.69 (0.20-6.09) |
| Colon | 19 | 1.09 | 65 | 1.09 | 132 | 0.97 | 216 | 1.02 (0.89-1.16) | 2 | 0.39 | 15 | 0.95 | 19 | 0.80 | 36 | 0.81 (0.56-1.12) |
| Rectum | 6 | 0.96 | 17 | 0.80 | 40 | 0.86 | 63 | 0.85 (0.65-1.09) | 0 | | 4 | 0.76 | 7 | 0.90 | 11 | 0.75 (0.37-1.34) |
| Liver | 0 | | 3 | 1.07 | 2 | 0.30 | 5 | 0.49 (0.16-1.15) | 0 | | 0 | | 0 | | 0 | |
| Gallbladder | 4 | 1.67 | 4 | 0.49 | 7 | 0.37‡ | 15 | 0.51 (0.29-0.84) | 0 | | 2 | 0.92 | 0 | | 2 | 0.33 (0.04-1.18) |
| Pancreas | 5 | 0.93 | 13 | 0.71 | 30 | 0.70 | 48 | 0.72 (0.54-0.96) | 1 | 0.63 | 3 | 0.61 | 4 | 0.54 | 8 | 0.57 (0.25-1.13) |
| Larynx | 0 | | 2 | 1.96 | 3 | 1.47 | 5 | 1.49 (0.48-3.47) | 0 | | 0 | | 0 | | 0 | |
| Lung | 17 | 1.45 | 53 | 1.36‡ | 102 | 1.23‡ | 172 | 1.29 (1.11-1.50) | 1 | 0.33 | 13 | 1.42 | 23 | 1.76‡ | 37 | 1.47 (1.03-2.02) |
| Connective, soft tissue | 0 | | 3 | 1.81 | 7 | 1.92 | 10 | 1.73 (0.83-3.17) | 0 | | 0 | | 0 | | 0 | |
| Cutaneous melanoma | 4 | 2.42 | 14 | 2.56‡ | 27 | 2.39‡ | 45 | 2.45 (1.78-3.27) | 5 | 12.4‡ | 2 | 1.63 | 5 | 2.82 | 12 | 3.52 (1.82-6.16) |
| Breast | 48 | 1.47‡ | 137 | 1.26‡ | 262 | 1.16‡ | 447 | 1.22 (1.11-1.34) | 12 | 1.49 | 27 | 1.10 | 34 | 0.96 | 73 | 1.07 (0.85-1.35) |
| Cervix | 3 | 0.88 | 7 | 0.63 | 4 | 0.19‡ | 14 | 0.39 (0.21-0.65) | 0 | | 3 | 1.38 | 1 | 0.33 | 4 | 0.67 (0.18-1.73) |
| Uterus | 12 | 1.49 | 27 | 1.01 | 50 | 0.93 | 89 | 1.01 (0.82-1.24) | 4 | 2.13 | 9 | 1.59 | 8 | 1.01 | 21 | 1.36 (0.84-2.07) |
| Ovary | 7 | 1.32 | 12 | 0.68 | 37 | 1.02 | 56 | 0.95 (0.72-1.23) | 0 | | 4 | 1.04 | 8 | 1.46 | 12 | 1.13 (0.58-1.98) |
| Bladder | 5 | 1.57 | 10 | 0.92 | 29 | 1.16 | 44 | 1.13 (0.82-1.51) | 0 | | 3 | 1.02 | 4 | 0.90 | 7 | 0.84 (0.34-1.73) |
| Kidney | 3 | 1.09 | 10 | 1.08 | 22 | 1.10 | 35 | 1.10 (0.76-1.52) | 1 | 1.36 | 2 | 0.88 | 2 | 0.61 | 5 | 0.79 (0.26-1.850) |
| Brain, nervous system | 1 | 0.65 | 7 | 1.38 | 14 | 1.34 | 22 | 1.29 (0.81-1.95) | 0 | | 1 | 0.87 | 1 | 0.61 | 2 | 0.63 (0.08-2.28) |
| Thyroid | 2 | 1.96 | 5 | 1.51 | 10 | 1.56 | 17 | 1.58 (0.92-2.53) | 0 | | 0 | | 0 | | 0 | |
| Without specification of site | 7 | 1.24 | 11 | 0.57 | 37 | 0.83 | 55 | 0.79 (0.59-1.03) | 1 | 0.60 | 3 | 0.58 | 9 | 1.14 | 13 | 0.88 (0.47-1.50) |
| Non-Hodgkin's lymphoma | 8 | 1.64 | 29 | 1.77‡ | 43 | 1.20 | 80 | 1.40 (1.13-1.75) | 6 | 4.57‡ | 5 | 1.23 | 9 | 1.51 | 20 | 1.77 (1.08-2.73) |
| Hodgkin's lymphoma | 1 | 2.38 | 1 | 0.72 | 1 | 0.35 | 3 | 0.65 (0.13-1.89) | 0 | | 0 | | 0 | | 0 | |
| Myeloma | 1 | 0.45 | 10 | 1.32 | 13 | 0.76 | 24 | 0.89 (0.57-1.32) | 0 | | 0 | | 1 | 0.34 | 1 | 0.18 (0.01-0.99) |
| Leukemia | 5 | 1.40 | 12 | 0.99 | 27 | 0.99 | 44 | 1.02 (0.74-1.24) | 3 | 3.00 | 7 | 2.25 | 7 | 1.52 | 17 | 1.95 (1.13-3.12) |

Abbreviation: SIR, standardized incidence ratio.

*ICD-9 codes for mouth: 141, 143, and 144; pharynx: 145-148; brain and nervous system: 191 and 192; without specification of site: 199; non-Hodgkin's lymphoma: 200 and 202; leukemia: 204-207.

†Total excluding NMSC includes sites not listed.

‡$P < 0.05$.

**Table 4. No. deaths and standardized mortality ratio in people with a history of BCC and SCC diagnosed with a second primary cancer (other than melanoma cancer) compared with patients who developed this cancer as their first primary**

| Site* | Male | | | | Female | | | |
|---|---|---|---|---|---|---|---|---|
| | BCC | | SCC | | BCC | | SCC | |
| | *n* | SMR (95% CI) | *n* | SMR (95% CI) | *n* | SMR (95% CI) | *n* | SMR (95% CI) |
| Total excluding NMSC † | 1,891 | 1.09 (1.04-1.14) | 647 | 1.18 (1.09-1.27) | 934 | 1.24 (1.16-1.32) | 192 | 1.55 (1.35-1.79) |
| Lip | 49 | 1.04 (0.77-1.38) | 45 | 1.54 (1.12-2.07) | 12 | 1.14 (0.59-1.99) | 5 | 3.23 (1.05-7.53) |
| Mouth, pharynx | 51 | 1.71 (1.27-2.25) | 19 | 2.67 (1.61-4.17) | 16 | 1.62 (0.92-2.62) | 1 | 6.34 (0.16-35.3) |
| Esophagus | 20 | 2.02 (1.23-3.11) | 4 | 3.97 (1.08-10.2) | 8 | 5.02 (2.17-9.90) | 2 | 6.23 (0.75-22.5) |
| Stomach | 76 | 1.05 (0.84-1.31) | 30 | 1.01 (0.68-1.44) | 32 | 1.31 (0.90-1.85) | 11 | 1.47 (0.73-2.63) |
| Small intestine | 1 | 0.29 (0.01-1.61) | 1 | 0.24 (0.03-1.67) | 7 | 1.55 (0.62-3.20) | 1 | 0.60 (0.08-4.28) |
| Colon | 160 | 1.22 (1.04-1.43) | 48 | 1.15 (0.85-1.53) | 116 | 1.27 (1.05-1.52) | 22 | 1.58 (0.99-2.39) |
| Rectum | 65 | 0.87 (0.68-1.11) | 24 | 1.18 (0.76-1.75) | 31 | 1.11 (0.76-1.58) | 10 | 4.05 (1.94-7.45) |
| Liver, gallbladder, pancreas | 79 | 1.47 (1.18-1.84) | 22 | 1.44 (0.90-2.19) | 53 | 1.62 (1.22-2.12) | 8 | 1.52 (0.66-3.00) |
| Larynx | 23 | 1.02 (0.65-1.53) | 9 | 2.72 (1.24-5.17) | 3 | 2.50 (0.52-7.31) | — | |
| Lung | 448 | 1.17 (1.07-1.29) | 143 | 1.10 (0.93-1.29) | 133 | 1.04 (0.88-1.24) | 31 | 1.55 (1.05-2.20) |
| Connective, soft tissue | 9 | 1.73 (0.79-3.28) | 5 | 2.84 (0.92-6.62) | 7 | 1.45 (0.69-3.03) | — | |
| Cutaneous melanoma | 33 | 1.08 (0.74-1.52) | 9 | 0.71 (0.32-1.34) | 16 | 1.37 (0.78-2.23) | 4 | 1.12 (0.31-2.88) |
| Female Breast | — | | — | | 185 | 1.02 (0.88-1.18) | 34 | 1.45 (1.00-2.02) |
| Cervix | — | | — | | 9 | 3.29 (1.50-6.24) | 3 | 2.78 (0.57-8.13) |
| Uterus | — | | — | | 41 | 1.44 (1.04-1.96) | 6 | 0.98 (0.36-2.13) |
| Ovary | — | | — | | 42 | 1.89 (1.36-2.55) | 5 | 0.79 (0.26-1.84) |
| Prostate | 389 | 0.85 (0.77-0.94) | 137 | 1.07 (0.91-1.27) | — | | — | |
| Kidney, bladder | 147 | 1.19 (1.01-1.39) | 48 | 1.85 (1.36-2.45) | 33 | 0.91 (0.62-1.28) | 7 | 1.81 (0.73-3.73) |
| Brain, nervous system | 27 | 1.27 (0.84-1.85) | 5 | 3.68 (1.20-8.60) | 18 | 2.28 (1.35-3.60) | 1 | 15.0 (0.38-83.6) |
| Thyroid | 2 | 2.16 (0.26-7.80) | 0 | | 6 | 1.52 (0.56-3.30) | 0 | |
| Without specification of site | 85 | 1.92 (1.55-2.37) | 26 | 1.36 (0.89-1.99) | 47 | 2.59 (1.90-3.44) | 9 | 3.16 (1.45-6.00) |
| Non-Hodgkin's lymphoma | 87 | 1.15 (0.93-1.42) | 29 | 0.92 (0.62-1.33) | 45 | 0.96 (0.70-1.29) | 14 | 1.97 (1.08-3.31) |
| Hodgkin's lymphoma | 4 | 3.21 (0.87-8.21) | 3 | 13.96 (2.88-40.8) | 1 | 0.94 (0.02-5.26) | — | |
| Myeloma | 44 | 1.03 (0.75-1.38) | 13 | 0.65 (0.35-1.12) | 14 | 0.90 (0.49-1.52) | 0 | |
| Leukemia | 64 | 1.37 (1.05-1.74) | 18 | 1.50 (0.89-2.37) | 26 | 0.84 (0.55-1.23) | 12 | 0.77 (0.40-1.34) |

Abbreviation: SMR, standardized mortality ratio.
*ICD-9 codes for mouth: 141, 143, and 144; pharynx: 145-148; brain and nervous system: 191 and 192; without specification of site: 199; other melanoma: 200 and 202; leukemia: 204-207.
†Total excluding NMSC includes sites not listed.

If people were leaving the province, the risk of a second primary would seem to decrease with time simply due to these lost-to-follow-up subjects. Due to incomplete coverage of registration with Manitoba Health, no censoring for emigration was undertaken. However, accurate follow-up of people is available from 1984 in Manitoba. Of the 17,371 people diagnosed with NMSC between 1984 and 2000, 97.0% (16,844) were still registered with Manitoba Health or had died at the

**Table 5. Result summary of studies that investigated the risk of second primary cancers in patients with a history of NMSC**

| Country | Data source | Maximum follow-up (y) | NMSC cases | Second primary ICD-9 codes* ($P < 0.05$) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 1 | 140 | 142 | 141, 143-148 | 150 | 151 | 152 | 153, 154 | 155, 156 |
| First primary: BCC | | | | | | | | | | | | |
| England (26) | CR | 14 | 13,961 | D † | N/A | N/A | | | | | | |
| Switzerland (14) | CR | 21 | 11,878 | D ‡ | | I ‡ | | D | D | | D | D |
| Denmark (8) | CR | 14 | 37,674 | I | I ‡ | I † | | | | | I ‡ | |
| Finland (7) | CR | 42 | 71,924 | I | I | I | I ‡ | | I † | I | I | I ‡ |
| United States (25) | MCP | 24 | 3,164 | I | | | I ‡ | | | | | |
| Canada§ | CR | 45 | 28,791 | I | I | I ‡ | I ‡ | D ‡ | D | | D ‡ | D † |
| Fist primary: SCC | | | | | | | | | | | | |
| Switzerland (15) | CR | 21 | 4,639 | | I ‡ | | | | | | D | |
| Denmark (27) | CR | 13 | 5,100 | I | I | I ‡ | I ‡ | | | I ‡ | | |
| Sweden (6) | CR | 35 | 25,974 | I | I | I | I ‡ | I † | I | | I | I † |
| England | CR | 40 | 25,731 | I | I | I | I † | I ‡ | | | I | I ‡ |
| Canada§ | CR | 45 | 8,786 | I ‡ | I | I ‡ | | | | | | |
| First primary: all NMSC excluding BCC | | | | | | | | | | | | |
| Finland (16) | CR | 27 | 5,438 | I | I | I | | | | | | |
| First primary: any NMSC | | | | | | | | | | | | |
| Bulgaria (28) | CR | 7 | 2,620 | | N/A | N/A | I | | D | | | |
| United States (3) | WHI † | 6 | 7,554 | I | | | I | | I | I | I | I |

NOTE: Studies with less than ~3,000 cases of BCC or SCC (4, 24, 29–32) were not included in the table.
Abbreviations: CR, cancer registry; MCP, medical care program; WHI, Woman Health Initiative Study; I, increased risk of cancer in NMSC cases compared to the general population; D, decreased.
*1, noncutaneous cancers or cancers other than NMSC; 140, lip; 142, salivary glands; 141 and 143-148, mount and/or pharynx; 150, esophagus; 151, stomach; 152, small intestine; 153-154, colon and/or rectum; 155 and 156, liver and/or gallbladder; 162, lung; 170, bone; 172, skin melanoma; 174, breast (female); 180, cervix; 182, body of uterus; 183, ovaries; 184, other female genital organs; 185, prostate; 188, bladder; 189, kidney; 190, eye; 191-192, brain and nervous system; 193, thyroid; 200 and 202, non-Hodgkin's lymphoma; 201, Hodgkin's disease; 203, myeloma; 204-207, leukemia.
†In women only.
‡In men only.
§Present study.

end of 2001. A further 354 (2.0%) moved to other Canadian provinces, and 143 were lost to follow-up. Failure to follow patients in this relatively old group of people does not seem to be a source of a large potential bias.

The risk of a second primary cancer was previously reported to be greater than expected in younger patients with a history of BCC or a SCC but not in older patients (6-8, 15). This observation was reported with other first primaries than NMSC as well (16-18). Similar results were found in the present study. To our knowledge, there is no clear explanation for this observation, but hypotheses, including genetic susceptibility and/or higher exposure to risk factors in younger age, have been suggested.

The risk of death in cancer patients with and without a history of NMSC has seldom been investigated. One study found that the risk of dying following non-Hodgkin's lymphoma, colon, breast, and prostate cancer (the only five cancer sites investigated in that study) was higher in patients with a SCC history (9). A second study found that risk of death following cutaneous melanoma, salivary glands, pharynx, lung, prostate, testis, and bladder cancer, as well as non-Hodgkin's lymphoma and leukemia was increased in patients with a history of NMSC (any morphology; ref. 11). Finally, a third one found that the risk of death following non-Hodgkin's lymphoma but not from colon cancer (the only two sites investigated) was greater in patients with a history NMSC (any morphology; ref. 10). It is difficult to compare the present study with previous ones because of the differences in study design or the number of cancer sites investigated, although the results seem comparable. One exception is prostate cancer, for which the risk of death, in our study, was reduced in patients with a BCC history.

An association between NMSC and a second primary could be the result of many factors, including adverse toxic effects of treatments, shared etiologic factors, random effects, false associations resulting from confounding variables, or biased ascertainment of new primaries as a result of increase surveillance in patients with a history of NMSC (19). It is unlikely, however, that the use of toxic drugs or radiation has a significant contribution in the risk of second primary because NMSC are usually treated with local procedures with limited systemic effect (20, 21). The predominant risk factor for NMSC is sun exposure. Cumulative sunlight exposure during adulthood is associated with an increased risk of SCC, whereas intense and short exposure is associated with BCC. Exposure to UV radiation is a well-established etiologic factor involved in the genesis of NMSC and cutaneous melanoma (22) and a potential one for non-Hodgkin's lymphoma. Exposure to UV light has been linked to non-Hodgkin's lymphoma through immune system suppression (23), although the relationship is weak. It was also hypothesized that risk factors, including smoking, ionizing radiation, and genetic predisposition, could be involved in the etiology of NMSC and other cancers. However, the concomitant contribution of these factors in the etiology of several cancers remains speculative.

It can not be excluded that chance alone played a role in the significance or nonsignificance of the present results, particularly for cancer sites with a small number of cases or deaths.

Similar to other studies based on cancer registries, the present one lacks information on potential etiologic and confounding factors. However, the studies from the United States that investigated the risk of second primary (3, 4, 24, 25) and the risk of death (11) in people with a NMSC history collected information on a wide range of individual characteristics that allowed for an assessment of potential confounders. They unanimously found that accounting for other risk factors in the analyses had little effect on the risk of cancer in patients with and without a history of NMSC. Thus, it is unlikely that the inclusion of confounding factors in the present analyses would have resulted in dramatically different results.

Patients are usually closely followed after a cancer diagnosis and could be subject to a surveillance bias leading to the diagnosis of a second primary. To estimate if NMSC patients were subject to such a bias, we examined the tumor stage of breast cancer cases with and without a history of NMSC, as well as the risk of being diagnosed with an *in situ* cervical cancer following a NMSC diagnosis. We hypothesized that if NMSC patients were subject to a surveillance bias, they were more likely to be diagnosed at an early stage and/or would have a higher risk of being diagnosed with an *in situ* cancer. Our results do not support that the long-term closer follow-up of NMSC patients may have been subjected to contribute to an earlier diagnosis of second primaries. However, we can not exclude that a diagnosis of NMSC may have contributed to higher rates of second primary within the few first months after a NMSC diagnosis. It is unlikely that this general conclusion could apply for tumors, such as cutaneous melanoma or lip cancer, as the same screening procedure is used for NMSC and these cancers.

**Table 5. Result summary of studies that investigated the risk of second primary cancers in patients with a history of NMSC (Cont'd)**

| 162 | 170 | 172 | 174 | 180 | 182 | 183 | 184 | 185 | 188 | 189 | 190 | 191, 192 | 193 | 200, 202 | 201 | 203 | 204-207 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | I | D | D | | | | D | D‡ | | | | | | | | |
| | | I | I | | | | | | | | | D | | I | | | |
| I | | I | I | | | | | | | I‡ | | | | I‡ | | | I‡ |
| I‡ | I‡ | I | I | | | | | I | I‡ | I‡ | I† | I | | I | | I‡ | I |
| I† | | I | I | | | | | | | I‡ | | | | | | | |
| I | | I | I | D | | | | I | | | | | | I | | I‡ | |
| I | | | | | | | | | | | | | | | | | |
| I | | I | | | | | | | | | | | | I | | | |
| I | | I‡ | | | | | | | | | | | | I‡ | | | I |
| I† | | I | | | I | | | | | | | I | I† | | I | | |
| | | I | | | | | | | | | | | | I | | | I† |
| | | I | | | | | | | | | | | | I | | I‡ D† | I† |
| | | I | | | | | | | | | | | | | | | |
| | | I | | | | | | I | | | | | | I‡ | | | I‡ |
| | | | | D | | | | | | | | | | | | | |
| I | I | I | I | I | | | | | | I | I | I | I | | I | | |

The present study has limitations regarding the assessment of people's history of NMSC. Not all cases of NMSC are reported to the Manitoba Cancer Registry, because tissue is not always submitted for pathologic evaluation when skin lesions are removed. As cancers following NMSC were completely recorded, this has no effect on the estimation of risk. In addition, it was not possible to assess the effect of multiple BCC or SCC on the risk of a second primary or the risk of a previous NMSC on the risk of a subsequent one. Karagas et al. (24) examined this and found that patients with multiple BCCs had a nonsignificant increased risk of a second primary compared with those with only one previous BCC.

The present findings provide insight into disease etiology and have implication for clinical follow-up and management of NMSC patients. They suggest that NMSC may share at least some risk factors with cutaneous melanoma, mouth and pharynx cancers, lung cancer, breast cancer, non-Hodgkin's lymphoma, and leukemia. To date, the most consistent explanation for this link is exposure to UV radiation, through intense and/or cumulative exposure or its immunosuppressive effect. However, further research needs to be conducted to clarify the complex underlying mechanisms. The present results also raise questions regarding medical follow-up protocols for individuals with a history of NMSC. Because the risk of second primary is modestly higher in people with a NMSC history and because the relationship between NMSC and other cancer is mostly speculative, special follow-up, beyond the generally accepted periodic examination of the skin, is not usually recommended. The present study supports this recommendation but indicates that special attention should be given to the early detection of cutaneous melanoma, head and neck cancers, lung cancer, breast cancer, and leukemia.

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# Risk of Second Primary Cancer and Death Following a Diagnosis of Nonmelanoma Skin Cancer

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