Occurrence of Other Cancers among Patients with Prior Basal Cell and Squamous Cell Skin Cancer[1]

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Abstract

Epidemiological studies suggest that individuals with basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin are more likely to develop other malignancies; however, the factors responsible for this are unknown. To clarify the risk of other cancers following the occurrence of BCC and SCC, we followed participants in a multicenter skin cancer prevention trial for subsequent malignancies. The study group consisted of 1805 BCC and SCC patients who had enrolled in a trial testing the efficacy of oral β-carotene. Medical confirmation was sought for all cancers (other than BCC or SCC), which were reported by participants or their next-of-kin over a follow-up period of 10 years. We computed the rate ratio (RR) and 95% confidence interval (CI) of time to first new, primary cancer in relation to history of BCC and SCC, using a proportional hazards model. A total of 235 participants had a new primary invasive cancer during 13,887 person-years of follow up. The risk of other cancers was modestly elevated in patients with one or more previous SCCs compared with those who only had a history of BCC (adjusted RR, 1.37; 95% CI, 0.91–2.07). Risk of other cancers also appeared to be increased among those who had multiple prior BCCs relative to those who had only one prior BCC (adjusted RR, 1.21; 95% CI, 0.91–1.61). Further adjustment for smoking history, Quetelet index, radiotherapy, extent of actinic skin damage, treatment assignment, or baseline β-carotene concentrations did not appreciably alter the results. Cancer of the respiratory system was most strongly related to previous SCC or multiple BCC [RRs (95% CI), 2.20 (1.05–4.62) and 2.34 (1.14–4.83), respectively]. Our data suggest that unidentified exposures or inherited risk factors may play a common etiological role in the pathogenesis of nonmelanoma skin cancer and other cancers, especially respiratory cancers, although larger studies would be necessary to exclude the role of chance in these findings.

Introduction

There are limited epidemiological data concerning the possibility that individuals with BCC[3] and SCC of the skin are at an elevated risk of developing other malignancies. Two reports from a large cohort of SCC and BCC patients identified from the Danish Cancer Registry found that rates of other cancers were 15–30% higher than expected from the general population incidence rates (1, 2). Primary malignancies of the respiratory tract and oral cavity, non-Hodgkin's lymphoma and melanoma were among the cancers that had a higher incidence. These reports raised several plausible hypotheses for the associations, including the possibility of shared etiological factors (*e.g.*, cigarette smoking and sunlight exposure). However, these factors could not be taken into account in these studies that were based on medical records or cancer registry information. Using data from a clinical trial of skin cancer prevention, we examined the risk of other cancers after the occurrence of BCC and SCC, while accounting for the contribution of other relevant risk factors.

Materials and Methods

Study participants had entered into a large multicenter skin cancer prevention trial described in detail previously (3). Briefly, individuals diagnosed with at least one BCC or SCC between January 1980 and February 1986 were recruited into a randomized trial to test whether oral β-carotene supplementation (50 mg/day) would reduce new skin cancer occurrences. A total of 5232 potentially eligible patients were identified from the dermatology and pathology records of medical centers in Hanover, NH; Los Angeles, CA; San Francisco, CA; and Minneapolis, MN. Of these, 1805 fulfilled study criteria and were enrolled (3). Excluded from the study were patients 85 years of age or older, women of child-bearing potential, and those with xeroderma pigmentosum, basal cell nevus syndrome, known arsenic exposure, or a medical condition that might limit their participation in the trial, including an active malignancy. Written informed consent was obtained for all participants.

At enrollment, participants completed a questionnaire regarding personal characteristics and habits including use of tobacco and a limited medical history (*e.g.*, radiotherapy). They also were seen by a study dermatologist who evaluated the

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[3] The abbreviations used are: BCC, basal cell carcinoma; SCC, squamous cell carcinoma; NMSC, nonmelanoma skin cancer; RR, relative risk; CI, confidence interval.

extent of actinic skin damage (classified as mild, moderate, or severe) and recorded the number and histological type of previous NMSCs. Every 3 months after randomization, we asked about hospitalizations and physician visits for any medical condition. Participants received study agents and were actively followed with skin exams until September 30, 1989, when the treatment phase of the study ended. Two study centers were located in regions included in the Surveillance Epidemiology and Ends Results program of the National Cancer Institute: University of California-Los Angeles and University of California-San Francisco. By verifying self-reported cancers, we identified 107 invasive cancers from these centers; only one additional invasive cancer (<1%) was found by the Surveillance Epidemiology and Ends Results registries that was not reported by the study participant or next of kin.

In 1991, we sent a follow-up questionnaire asking participants whether they had ever been told by a doctor that they had cancer and, if so, to indicate: (*a*) the type of cancer; (*b*) when it was diagnosed; and (*c*) the name and address of the doctor providing care for the cancer. A second follow-up questionnaire was sent in 1993 requesting information on the occurrence of cancers since the last follow-up (or during their entire lifetime for those who did not respond to the first follow-up survey). We asked this information of the next-of-kin for participants who died during the follow-up period.

We sought medical confirmation on all reported cancers that occurred after randomization. Cancers were considered medically verified if we obtained confirmation from either a physician (pathologist or treating physician) or medical record (including tumor registry data). For each new cancer, we coded the anatomical site and histological type of the tumor according to the International Classification of Diseases for Oncology, recorded the level of confirmation (*i.e.*, microscopic, clinical, autopsy, or death certificate), and documented the month and year the cancer was diagnosed.

In our analyses, we examined the risk of other cancers in relation to the number and histological type of NMSCs before randomization. To evaluate the overall risk of cancer associated with a history of SCC, we compared the risk of cancer among those who did and did not have a SCC before randomization. Because all participants in our study had at least one prior NMSC at enrollment, by definition, those who did not have a prior SCC had a history of at least one BCC. Therefore, we further examined the risk associated with multiple BCCs before enrollment as compared with only one prior BCC; too few patients had more than one prior SCC to permit analysis by number of SCC.

We computed RRs and 95% CIs for time to first cancer using a Cox proportional hazards model and assessed the potentially confounding or modifying effects of age at study entry, sex, study center, smoking history, Quetelet index (weight in kg/height in m^2), extent of actinic skin damage, history of radiation therapy, baseline plasma β-carotene, and treatment assignment. In these analyses, we counted only the first invasive cancer occurrence in a given individual. We also considered risks according to whether the first NMSC was diagnosed before or after age 60. For those who had a history of both BCC and SCC, we could not determine whether the BCC or SCC was diagnosed first; however, among those with BCC only, the age of first NMSC represented the first BCC diagnosis. Log-log survival plots were examined to verify the proportional hazards assumption.

Data were censored at the date of the individual's last contact or the end of the second follow-up period, March 1, 1993. As study outcomes, we included reported cancers verified as histologically confirmed primary invasive cancers. We excluded cancers that either were metastases from a NMSC or other cancer, occurred before randomization, were documented solely at autopsy or on the death certificate, or lacked histopathological confirmation. We separately examined cancers grouped according to International Classification of Diseases for Oncology (first edition) codes as: oral cavity and pharynx (140–149), digestive system (150–159), respiratory system (160–165), bone and soft tissues (170–171), skin (other than NMSC; 173), breast (174), female genital system (179–184), male genital system (185–187), urinary system (188–189), eye and nervous system (190–192), and leukemias and lymphomas (169 and 196). In each of these analyses, we computed the time to the first occurrence of each type of cancer. Thus, individuals who had multiple primary cancers could have been included in the analysis of more than one type of cancer.

Results

Of the 1805 study participants, 1735 had a history of at least one BCC, and 146 had a history of SCC at enrollment; these figures include the 86 participants who had both BCC and SCC. The mean age of the study group was 63.1 years (SD, 10.0 years), and 69% were men. The distribution of patient characteristics differed slightly by history of BCC or SCC (Table 1). Those who had a history of SCC tended to be older than those who had BCC, and a higher proportion were men (Table 1). A larger proportion of patients who had SCC or multiple BCCs had severe actinic skin damage compared with those who had only one prior BCC. The distribution of Quetelet index, cigarette smoking, and treatment assignment were roughly similar among patients with a history of BCC and SCC. Radiotherapy was reported more often among those who had a history of multiple BCCs compared with those who had only one prior BCC.

Participants were followed for new cancers an average of 7.7 years (median, 8.2 years; range, less than 1 month to 10 years), accruing a total of 13,966 person-years. One hundred and fifty-one participants (8%) died during the trial. Of the remaining 1654 individuals, 24 (1%) refused to answer the follow-up questionnaire or could not be located. An additional 162 (9%) individuals died during the postintervention follow-up period; we obtained consent to review medical records from the next-of-kin for all but 12 of these individuals (1% of the total sample).

Study participants or their next-of-kin reported 372 cancers, of which 274 (74%) were medically verified, postrandomization, primary cancers (other than NMSC; Table 2). The remaining reported cancers were recurrences or metastases from a cancer diagnosed before randomization or a noncancer diagnosis (Table 2). The medical records for only 2% (9 of 372) of reported cancers could not be located (Table 2). There were a total of 265 microscopically confirmed cancers (97% of the documented cancers; Table 2), of which 158 (60%) were diagnosed up to September 30, 1989, and 107 (40%) were diagnosed between October 1, 1989 and March 1, 1993. Only a small fraction (4%) of microscopically confirmed cancers were *in situ* tumors (Table 2).

Participants who had one or more previous SCCs had an elevated, although not statistically significant, relative risk for other cancers compared with those who had no history of SCC (RR, 1.37; 95% CI, 0.91–2.07). The risk of other malignancies also appeared to be increased among those who had multiple BCCs in the past relative to those who had only one prior BCC (RR, 1.21; 95% CI, 0.91–1.61). RRs were initially adjusted for

Table 1 Selected characteristics of study participants according to history of BCC or SCC[a]

	Any prior SCC (n = 146) n (%)	One prior BCC[b] (n = 794) n (%)	Multiple prior BCCs[b] (n = 855) n (%)
Age, y			
<60	27 (18)	299 (38)	220 (26)
60–69	70 (48)	310 (39)	397 (46)
≥70	49 (34)	185 (23)	238 (28)
Sex			
Male	119 (82)	525 (66)	597 (70)
Female	27 (18)	269 (34)	258 (30)
Study center			
Hanover	24 (16)	203 (26)	210 (25)
Los Angeles	22 (15)	103 (13)	219 (26)
San Francisco	42 (29)	108 (14)	143 (17)
Minneapolis	58 (40)	380 (48)	283 (33)
Extent of actinic damage			
Mild	26 (18)	296 (37)	202 (24)
Moderate	88 (61)	446 (56)	507 (60)
Severe	30 (21)	50 (6)	137 (16)
Unknown	2	2	9
Quetelet index (kg/m^2)			
<23	38 (27)	219 (28)	218 (26)
23–27	72 (50)	357 (46)	407 (48)
≥27	33 (23)	206 (26)	216 (26)
Unknown	3	12	14
Cigarette smoking			
Never	56 (38)	282 (36)	310 (36)
Former	65 (45)	360 (45)	388 (45)
Current	25 (17)	150 (19)	157 (18)
Unknown	0	2	0
Prior radiation therapy			
No	115 (79)	696 (88)	611 (72)
Yes	31 (21)	97 (12)	242 (28)
Unknown	0	1	2
Treatment assignment			
β-carotene	76 (52)	388 (49)	443 (52)
Placebo	70 (48)	406 (51)	412 (48)
Plasma β-carotene at baseline (μM)			
<11.2	37 (26)	183 (23)	216 (26)
11.2–17.8	29 (20)	201 (26)	206 (25)
17.9–27.7	46 (32)	200 (26)	194 (24)
≥27.7	32 (22)	199 (25)	209 (25)
Unknown	2	11	30

[a] Ten individuals have unknown BCC and SCC history.
[b] Includes only those who had previous BCC but not SCC.

age, sex, and study center; further adjustment for smoking history, Quetelet index, extent of actinic skin damage, radiotherapy, treatment assignment, or baseline β-carotene concentrations did not appreciably alter the results. However, the excess risk of cancer associated with SCC appeared to be confined to patients who were younger than 60 years old when first diagnosed with NMSC. For BCC, the reverse was found; the RR was elevated only for those age 60 years or older at first BCC (Table 3). Exclusion of subjects who reported a history of cancer prior to randomization did not affect our RRs.

Of the specific cancer sites examined, cancer of the respiratory system was most clearly related to SCC (Table 4). Patients with multiple BCCs also appeared to be at higher risk of respiratory cancer (Table 4). Although much of the radiotherapy reported by this cohort was for benign dermatological conditions (4), we assessed the possibility that it could confound these results, because radiotherapy was found previously to be related to BCC in these data (4). However, the RR of respiratory cancer associated with multiple BCCs diminished only slightly after adjustment for radiotherapy (RR, 2.02; 95%

Table 2 Follow-up information on reported cancers among the skin cancer prevention trial enrollees

	No. of cancers	No. of individuals
Cancers reported	372	308
Medically verified cancers[a]	274	255
Microscopically confirmed	265	246
Invasive	254	235
In situ	11	11
Clinical diagnosis only	6	6
Death certificate diagnosis only	2	2
Autopsy diagnosis only	1	1
Not verified[b]	89	75
Record could not be located	9	8

[a] This includes new primary cancers other than NMSC occurring after randomization.
[b] Includes reported cancers that, upon review, were prerandomization cancers (n = 17), recurrence or metastases (n = 30), metastases from a NMSC (n = 4), or based on the medical record, was not a cancer (n = 38).

Table 3 RR (95% CI) of invasive cancers in relation to history of SCC and BCC of the skin according to age at diagnosis of first skin cancer[a]

	Individuals with cancer	Person-Years	RR[b] (95% CI)
Any prior SCC			
No (BCC only)	204	12,838	1.00 (reference)
Yes (one or more)	26	1,049	1.37 (0.91–2.07)
<60	19	653	1.83 (1.14–2.94)
≥60	7	385	0.83 (0.39–1.78)
Multiple prior BCCs[c]			
No (one only)	85	6,243	1.00 (reference)
Yes (multiple)	135	6,595	1.21 (0.91–1.61)
<60 y	59	4,327	1.03 (0.73–1.45)
≥60 y	62	2,233	1.51 (1.06–2.14)

[a] Ten individuals (six cancers) were excluded from the analysis because of missing information on history of NMSCs. Seven individuals (2 with SCC and 5 with BCC) are missing information on age at first NMSC.
[b] Age, sex and center-adjusted RR based on proportional hazards model with time to first cancer as the endpoint.
[c] Subjects with a history of SCC are excluded.

CI, 0.96–4.25). Of the 47 respiratory cancers, all but seven occurred in the trachea or bronchus (there were two cancers of the nasal cavity, four of the larynx, and one of the pleura). Adjustment for cigarette smoking history did not affect any of the risk estimates for respiratory cancer.

Risk of urinary cancers also appeared higher among SCC patients and in patients with multiple BCCs, but the results were highly imprecise (Table 4). There also were nonsignificant increases in the RRs for cancers of the oral cavity and pharynx, as well as for lymphomas and leukemias, among those with prior SCC. For female genital cancer, risk was nonsignificantly elevated among those with a history of multiple BCCs (Table 4).

With regard to sites of cancer that occurred infrequently in this population, the RR for non-Hodgkin's lymphoma associated with previous SCC was 2.03 (95% CI, 0.23–17.55) and for multiple BCCs was 0.53 (95% CI, 0.09–2.92). Colorectal cancer risk did not appear to be increased (RR with prior SCC, 0.87; 95% CI, 0.20–3.72; RR with multiple BCCs, 0.73; 95% CI, 0.33–1.64); there were only two occurrences of small intestine cancers. Melanomas (6 cutaneous and 3 ocular) and cancers of the breast (19 cases) occurred almost exclusively among those with a history of BCC.

Three participants developed salivary gland cancer, and two of these also developed prostate cancer. Six other participants had multiple primaries, which included prostate cancer: two had bladder cancer; two had lung cancer; and two had melanoma. No other combinations of cancers occurred more than once in a total of 18 participants who had multiple primaries.

Discussion

There has been uncertainty about the potential for developing other cancers among patients with Bowen's disease (SCC *in situ*), invasive SCC, and BCC of the skin (5). Part of the difficulty in studying these tumors is their exclusion from most population-based cancer registries. In two reports, the Danish Cancer Registry, which has historically included NMSCs, was used to link over 35,000 cases of BCC and 5,100 cases of SCC with subsequent cancers identified in the registry (1, 2). The overall observed number of subsequent cancers was greater than that expected in the Danish population (standardized incidence ratio, 1.13 for BCC and 1.3 for SCC). In an earlier study, Teppo *et al.* (6) evaluated the occurrence of cancers among 5538 men and women identified from the Finnish Cancer Registry with a diagnosis of skin cancer, other than BCC or melanoma (presumably largely SCC). They likewise observed about 20–30% excess cancer risk compared with the expected rates in the Finnish population. In contrast, Bowen's disease (n = 71), SCC (n = 169), and BCC (n = 657) patients had no increased risk of other cancers in a study based on medical records from the Mayo Clinic in Rochester, MN (7). This smaller study may have lacked power to detect an elevated cancer risk of the magnitude observed in the Danish and Finnish studies, however. In our study, which also had a limited sample size, the overall risks were comparable with those reported from the larger studies.

We found an increased incidence of respiratory cancers in subjects with a history of multiple BCCs or any history of SCC. These results are consistent with the Danish (1, 2) but not Finnish (6) studies. Frisch and colleagues (1, 2) hypothesized that the concomitant occurrence of these cancers could be due to cigarette smoking. We and others have found a relationship between tobacco smoking and incidence of SCC but not BCC (8–10). In contrast, an association between ionizing radiation has been found predominantly for BCC but not SCC (4, 11, 12). Inclusion of radiotherapy in our analysis had only a small effect on the risk estimates for respiratory cancers associated with prior BCC, and adjustment for cigarette smoking history had virtually no effect on any of our RR estimates.

In previous studies, BCC and SCC were related to risk of leukemias (1, 2, 13), non-Hodgkin's lymphoma (2, 6, 13), and cancers of the lip and salivary glands (1, 2, 6, 14). In analyses based on the Danish Cancer Registry (1, 2), an increased risk of kidney cancer was observed for BCC but not SCC. No association with urinary cancers was found in the Finnish study (6). Our study was too small to provide precise risk estimates for many types of tumors, although we found some evidence that urinary cancers were related to SCC and BCC and that history of SCC was related to non-Hodgkin's lymphoma.

Individuals homozygous for an autosomal recessive trait xeroderma pigmentosum have a predisposition to BCC and SCC at a young age, resulting from DNA excision repair defects; these individuals are also more prone to other malignancies (15). More subtle defects in DNA repair capacity have been related to BCC in one clinic-based case-control study (16), particularly among those diagnosed with BCC at age 40 years or younger. An age effect with regard to subsequent cancers was also observed by Frisch and colleagues (1, 2). In their studies, risk of other malignancies was most pronounced among those who were under age 60 years when their first BCC or SCC was diagnosed; we confirmed this finding among SCC, but not BCC, patients in our study.

Previous studies have relied on existing medical records, including linkage within cancer registries. One limitation of this approach is that the possible confounding effects of personal habits (*e.g.*, cigarette smoking), other exposures (*e.g.*, ionizing radiation), and sunlight-related risk factors could not be assessed. Moreover, record linkage studies do not readily permit an assessment of completeness of follow-up. We were able to actively follow skin cancer patients and to ascertain exposure and health history information from a questionnaire administered at study entry. Thus, we obtained relatively complete follow-up information and could evaluate the contribution of exposure history to the risks we detected.

Interpretation of our study is limited by the fact that all study participants had at least one prior NMSC. Because BCC is a far more common tumor than SCC in the regions we

Table 4 RR (95% CI) of specific types of invasive cancers in relation to history of SCC and BCC of the skin[a]

Specific site	Any prior SCC			Multiple prior BCC[b]		
	No (*BCC only*) individuals with cancer	Yes (*one or more*) individuals with cancer	RR[c] (95% CI)	No (*one only*) individuals with cancer	Yes (*multiple*) individuals with cancer	RR[d] (95% CI)
Oral/Pharynx	7	1	2.19 (0.26–18.39)[e]	0	7	
Digestive	39	3	0.84 (0.26–2.75)	18	21	1.01 (0.54–1.90)
Respiratory	38	9	2.20 (1.05–4.62)	10	28	2.34 (1.14–4.83)
Bone/Soft tissue	2	0		2	0	
Skin[f]	11	1	1.04 (0.13–8.18)	4	7	1.44 (0.42–4.94)
Breast	18	1	0.63 (0.08–4.75)[e]	8	10	1.06 (0.42–2.69)
Female genital	4	0		1	3	3.09 (0.31–30.41)
Male genital[g]	63	7	1.25 (0.57–2.75)[e]	28	35	1.06 (0.64–1.74)
Urinary	20	3	1.69 (0.49–5.80)	6	14	1.98 (0.76–5.17)
Eye/Nervous	4	0		3	1	0.30 (0.03–2.91)
Leukemia and lymphoma	10	2	2.68 (0.57–12.50)	5	5	1.06 (0.30–3.71)

[a] RRs are based on Cox model with time to first cancer as the endpoint. Ten individuals (six cancers) were excluded from the analysis because of missing information on history of NMSCs. Primary site could not be determined for four cancers. One person had both bladder and kidney cancers.
[b] Subjects with a history of SCC are excluded.
[c] Age (continuous), sex, and center adjusted.
[d] Age adjusted.
[e] Age and center adjusted.
[f] Skin cancers other than NMSC.
[g] All male genital cancers were prostate cancers.

studied, most participants had a history of BCC, even those who also had a SCC. Therefore, our findings for SCC may be conservative compared with what would be obtained in comparison with persons who never had an NMSC. For BCC, we were limited to the assessment of cancer risk among those who had BCC relative to those who had SCC (*e.g.*, the inverse of the rate ratios presented in Table 3). Increased cancer surveillance may account for some of the higher occurrence rates we and others observed among skin cancer patients, but this seems unlikely in our group of NMSC patients, who were uniformly followed.

In summary, we found that the excess cancer risk after SCC and multiple BCC occurrences could not be explained by exposure history such as cigarette smoking and ionizing radiation therapy. Although we cannot fully discount the role of chance as explanation for some of our findings, our results suggest that the occurrence of NMSC is linked to risk of respiratory cancer, and perhaps other cancers, and this link may reflect inherited factors or as yet unidentified exposures.

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