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Original Contribution

Are Patients with Skin Cancer at Lower Risk of Developing Colorectal or Breast Cancer?

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Ultraviolet exposure may reduce the risk of colorectal and breast cancer as the result of rising vitamin D levels. Because skin cancer is positively related to sun exposure, the authors hypothesized a lower incidence of breast and colorectal cancer after skin cancer diagnosis. They analyzed the incidence of colorectal and breast cancer diagnosed from 1972 to 2002 among 26,916 Netherlands skin cancer patients (4,089 squamous cell carcinoma (SCC), 19,319 basal cell carcinoma (BCC), and 3,508 cutaneous malignant melanoma (CMM)). Standardized incidence ratios were calculated. A markedly decreased risk of colorectal cancer was found for subgroups supposedly associated with the highest accumulated sun exposure: men (standardized incidence ratio (SIR) = 0.83, 95% confidence interval (CI): 0.71, 0.97); patients with SCC (SIR = 0.64, 95% CI: 0.43, 0.93); older patients at SCC diagnosis (SIR = 0.59, 95% CI: 0.37, 0.88); and patients with a SCC or BCC lesion on the head and neck area (SIR = 0.59, 95% CI: 0.36, 0.92 for SCC and SIR = 0.78, 95% CI: 0.63, 0.97 for BCC). Patients with CMM exhibited an increased risk of breast cancer, especially advanced breast cancer (SIR = 2.20, 95% CI: 1.10, 3.94) and older patients at CMM diagnosis (SIR = 1.87, 95% CI: 1.14, 2.89). Study results suggest a beneficial effect of continuous sun exposure against colorectal cancer. The higher risk of breast cancer among CMM patients may be related to socioeconomic class, both being more common in the affluent group.

breast neoplasms; colorectal neoplasms; risk; skin neoplasms; vitamin D

Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; CMM, cutaneous malignant melanoma; SCC, squamous cell carcinoma; SIR, standardized incidence ratio.

Colorectal and breast cancers are two of the most common cancers worldwide (1). Geographic variation in their occurrence has led to the theory of a beneficial effect of greater sun exposure on the incidence of and mortality from breast and colorectal cancers (2, 3). Because the majority of skin cancers are caused by exposure to ultraviolet radiation, we expect a lower risk of colorectal and breast cancers for skin cancer patients compared with the general population (4, 5).

The inverse association between ultraviolet exposure and some cancers—including breast and colorectal cancers—was derived mainly from ecologic studies, reporting a north-south gradient with higher cancer occurrence or mortality in less sunny areas compared with sunnier areas (2, 3, 6). These studies may have been confounded at the group level, being unable to adjust for regional differences between other risk factors. For example, fish intake may reduce the risk of colorectal cancer (7), and fish is probably more widely available in coastal areas where it is sunnier. Studies on the association between sunlight and cancer incidence or mortality with information on individual sun exposure generally found a preventive effect on breast and colorectal

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cancer (6). However, out of five case-control and cohort studies, only one demonstrated a significant reduction of death from breast or colorectal cancer. A meta-analysis of the risk of cancer after skin cancer showed a significant reduction of colon cancer among patients with previous squamous cell carcinoma of the skin, but not when stratified according to gender and not for breast cancer (8).

In this study, we investigated the association between sun exposure and risk of colorectal and breast cancers by assessing the risks of these cancers after skin cancer. Analyses were performed for all skin cancer patients combined, as well as stratified according to skin cancer type (squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and cutaneous malignant melanoma (CMM)). We expected to observe lower risks of colorectal and breast cancers among patients who are typically associated with more chronic sun exposure: patients with SCC, elderly skin cancer patients, and patients with skin cancer on the head or the neck area (9). Furthermore, we also examined the relative risk of breast and colorectal cancers according to the time since skin cancer diagnosis and stage of breast and colorectal cancers at the time of their diagnosis: If sunlight not only protects against the occurrence of cancer but also slows down the progression, then one would expect to see a decreased incidence of specifically advanced disease. In addition, we analyzed separately the risk for colon and rectal cancers following diagnosis of the three skin cancer types.

MATERIALS AND METHODS

Data

We retrieved data on patients with skin cancer who were diagnosed with a first primary in the southern Netherlands from 1972 to 2002. Data from patients were recorded within the framework of the population-based Eindhoven Cancer Registry that now covers almost 2.4 million inhabitants. The registry is regularly notified about new cancer cases by the pathology and hematology departments in the region. For nonmelanoma skin cancer, especially BCC, registration may be incomplete. However, in our registry, the dermatologist and pathologist regularly report such cases. Moreover, most general practitioners do not excise BCC regularly, and if they do they should send the material to the pathologist whose archive is directly linked to the registry (5). Detailed patient data were obtained from the hospitals, and active follow-up of vital status for each patient was conducted through the Central Bureau for Genealogy. Within this study, patients were followed until January 1, 2004, the date of a second primary cancer diagnosis, the date of death, or loss to follow-up. Follow-up for the vital status of patients with BCC was started in 1990; thus, for this cohort, the time at risk began in that year. Coding of multiple tumors was adopted from the rules proposed by the International Agency for Research on Cancer (10).

Statistical analysis

In order to determine whether skin cancer patients were at a higher or a lower risk of developing cancers than the general population, we compared the incidence of breast (females only) and colorectal (both sexes) cancers among these patients (observed incidence) with the incidence of the same tumors in the reference population. The expected incidence was calculated adjusting for gender, age (in 5-year age categories), and calendar time (for SCC and CMM: 1972–1977, 1978–1983, 1984–1989, 1990–1994, 1995–1999, and 2000–2004; for BCC: 1990–1992, 1993–1995, 1996–1998, 1999–2000, 2001–2002, 2003–2004) at skin cancer diagnosis. Standardized incidence ratios were computed by dividing the observed incidence rates by the expected incidence rate; 95 percent confidence intervals were calculated by use of exact Poisson probability (11).

We computed the standardized incidence ratio for 1) skin cancer type (SCC, BCC, and CMM); 2) sex (male and female); 3) age at diagnosis of skin cancer (aged <60 vs. ≥ 60 years); 4) location of skin cancer (the head and neck area (not including lip cancer) vs. other body sites); 5) colon and rectum, separately; 6) duration of follow-up until occurrence of breast or colorectal cancer (0–$<$1 year, 1–$<$2 years, 2–$<$3 years, 3–$<$4 years, 4–$<$5 years, and ≥ 5 years); and 7) stage of colorectal and breast cancers (colorectal: stages I and II vs. stages III and IV vs. unknown; similar for breast). The tumor, node, and metastasis (TNM) classification system was used.

We excluded patients with missing information on body site (unknown-location squamous cell carcinoma: $n = 20$ (0.5 percent); basal cell carcinoma: $n = 60$ (0.3 percent); cutaneous malignant melanoma: $n = 122$ (3.4 percent)). We finally had 26,916 patients with a previous skin cancer diagnosis in our analysis.

In addition, we calculated the risk of lung cancer for our skin cancer cohort to test the consistency of our hypothesis, since lung cancer has not been observed to be associated with sun exposure. On the contrary, we expected an increased risk of lung cancer in the cohort of SCC patients, because cigarette smoking is a risk factor for both (12). A decreased risk of lung cancer was expected among CMM patients, because the higher socioeconomic group, which has the highest CMM incidence, smoked less (13).

We quantified the mean relative risk and the range of risks of second colorectal and breast cancers after skin cancer for each skin cancer type separately from previously published studies (14–33). We included studies that were published between 1997 and 2007, categorized results by gender and skin cancer type, and presented relative risk estimates. We identified 19 studies (15–33); five studies were excluded because they used a different methodology (16, 21, 28) or presented results differently (15, 20), one study was excluded because the extremely wide confidence intervals led us to question the methodology (29), and data from one study overlapped with those of a more recent study, which was used instead (19, 33). For the study of Tuohimaa et al. (30), only the estimates based on the data of Spain, Singapore, and Australia were included, because estimates of the other countries (e.g., Finland, Sweden, and Canada) were taken from other studies (26, 27, 31).

RESULTS

Women were diagnosed more frequently with CMM but less often with SCC. SCC and BCC patients were generally

TABLE 1. Characteristics of southern Netherlands patients with skin cancer diagnosed in 1972–2002*

	Skin cancer types			Total
	Squamous cell carcinoma	Basal cell carcinoma	Cutaneous melanoma	
No. of person-years	21,098	111,098	24,091	156,287
No. of patients (% of total)	4,089 (15)	19,319 (72)	3,508 (13)	26,916
Median age, years				
At skin cancer diagnosis	74.1†	65.6	50.8	65.6
At colorectal cancer diagnosis	75.4	74.7	68.0	74.3
At breast cancer diagnosis	72.6	68.1	64.4	67.9
Median follow-up, years	3.8	5.2	5.4	5.0
Gender, no. (%)				
Male	2,620 (64)	9,501 (49)	1,420 (40)	13,541 (50)
Female	1,469 (36)	9,818 (51)	2,088 (60)	13,375 (50)
Age at diagnosis, no. (%)				
<60 years	610 (15)	7,094 (37)	2,422 (69)	10,126 (38)
≥60 years	3,479 (85)	12,225 (63)	1,086 (31)	16,790 (62)
Location, no. (%)				
Head and neck	2,975 (73)	14,248 (74)	497 (15)	17,720 (67)
Other	1,094 (27)	5,011 (26)	2,889 (85)	8,994 (33)
Second cancers, no.				
Colorectal	43	224	24	291
Female breast	22	174	40	236
Total	65	398	64	527

* Basal cell carcinoma patients derived from patients diagnosed in 1990–2002.
† Female patients with squamous cell carcinoma who developed second breast cancer were diagnosed with the former at a median age of 69.7 years.

older than CMM patients, and lesions were found more often on the head and neck area (table 1). Of the 4,089 patients with SCC, 43 and 22 were diagnosed with colorectal and breast cancers, respectively, during 21,098 person-years of follow-up. Among 19,319 BCC cases with a follow-up of 111,098 person-years, a total of 224 colorectal and 174 breast cancers were diagnosed, and among 3,508 CMM patients, 24 and 40 were subsequently diagnosed with colorectal and breast cancers, respectively.

Table 2 shows the numbers of colorectal cancer cases occurring in the skin cancer cohorts and the corresponding standardized incidence ratios for men and women together and separately according to various tumor characteristics. We observed a decreased risk of colorectal cancer, especially among men with a previous SCC, compared with the general population (standardized incidence ratio (SIR) = 0.64, 95 percent confidence interval (CI): 0.43, 0.93). Men who were older than 60 years at SCC diagnosis (SIR = 0.59, 95 percent CI: 0.37, 0.88) and who were diagnosed with SCC on the head or neck area (SIR = 0.59, 95 percent CI: 0.36, 0.92) showed a significantly lower risk of colorectal cancer. In addition, males diagnosed with BCC on the head and neck exhibited a lower risk of colorectal cancer compared with the general population (SIR = 0.78, 95 percent CI: 0.63, 0.97). SCC and BCC patients exhibited a significantly decreased risk of colorectal cancer at stages I and II. The separate standardized incidence ratio estimates for colon and rectal cancer after skin cancer are presented in table 3. A 35 percent lower risk of colon cancer in patients with SCC as compared with the general population was observed (SIR = 0.64, 95 percent CI: 0.42, 0.94).

The standardized incidence ratio of breast cancer among women previously diagnosed with skin cancer is given in table 4. SCC patients showed a lower breast cancer risk compared with the other skin cancer types, with a standardized incidence ratio of 0.87 versus 0.99 and 1.19 among SCC, BCC, and CMM patients, respectively. Standardized incidence ratios tended to be lower among those diagnosed with SCC after the age of 60 years (in patients ≥60 years vs. <60 years: SIR = 0.66 vs. 1.98) and when SCC was located on the head and neck area (SCC on the head and neck area vs. on other body parts: SIR = 0.79 vs. 0.92). More than two thirds of the women were diagnosed with breast cancer stages I and II. Those diagnosed with BCC showed a decreased risk of breast cancer stages III and IV as compared with the general population (SIR = 0.53, 95 percent CI: 0.30, 0.88). In contrast, CMM patients had an increased risk of breast cancer stages III and IV as compared with the general population (SIR = 2.20, 95 percent CI: 1.10, 3.94). Older CMM patients exhibited a 90 percent higher

TABLE 2. Standardized incidence ratios for southern Netherlands patients with colorectal cancer diagnosed in 1972–2004 following skin cancer, according to gender*

	Total			Men			Women		
	No. of cases	Standardized incidence ratio	95% confidence interval	No. of cases	Standardized incidence ratio	95% confidence interval	No. of cases	Standardized incidence ratio	95% confidence interval
All skin cancers	291	0.89	0.79, 0.99	162	0.83	0.71, 0.97	129	0.97	0.81, 1.15
Squamous cell carcinoma	43	0.69	0.50, 0.94	28	0.64	0.43, 0.93	15	0.81	0.45, 1.34
Basal cell carcinoma	224	0.93	0.81, 1.06	122	0.87	0.73, 1.04	102	1.01	0.82, 1.22
Cutaneous melanoma	24	0.95	0.61, 1.42	12	1.05	0.54, 1.83	12	0.87	0.45, 1.52
Squamous cell carcinoma									
Age at diagnosis									
<60 years	8	1.38	0.60, 2.72	5	1.15	0.37, 2.69	3	2.05	0.42, 6.00
≥60 years	35	0.62	0.43, 0.87	23	0.59	0.37, 0.88	12	0.71	0.36, 1.23
Location									
Head and neck	32	0.70	0.48, 0.99	20	0.59	0.36, 0.92	12	0.98	0.51, 1.71
Other	11	0.70	0.35, 1.26	8	0.83	0.36, 1.64	3	0.50	0.10, 1.45
Colorectal cancer stage									
I and II	20	0.63	0.38, 0.97	12	0.53	0.27, 0.92	8	0.87	0.38, 1.72
III and IV	16	0.71	0.40, 1.15	10	0.64	0.30, 1.17	6	0.87	0.32, 1.90
Unknown	7	0.93	0.38, 1.93	6	1.19	0.44, 2.60	1	0.41	0.01, 2.26
Basal cell carcinoma									
Age at diagnosis									
<60 years	39	1.08	0.77, 1.48	23	1.12	0.71, 1.68	16	1.03	0.59, 1.68
≥60 years	185	0.90	0.78, 1.04	99	0.83	0.68, 1.01	86	1.00	0.80, 1.24
Location									
Head and neck	167	0.88	0.75, 1.02	87	0.78	0.63, 0.97	80	1.00	0.80, 1.25
Other	56	1.13	0.85, 1.47	35	1.25	0.87, 1.74	21	0.98	0.61, 1.50
Colorectal cancer stage									
I and II	94	0.75	0.61, 0.92	57	0.77	0.58, 0.99	37	0.72	0.51, 1.00
III and IV	114	1.19	0.99, 1.44	56	1.03	0.78, 1.34	58	1.42	1.08, 1.84
Unknown	16	0.79	0.31, 1.29	9	0.83	0.38, 1.58	7	0.75	0.30, 1.54
Cutaneous melanoma									
Age at diagnosis									
<60 years	11	1.06	0.53, 1.89	6	1.37	0.50, 2.99	5	0.83	0.27, 1.94
≥60 years	13	0.88	0.47, 1.50	6	0.85	0.31, 1.85	7	0.90	0.36, 1.85
Location									
Head and neck	5	0.95	0.31, 2.22	3	1.05	0.22, 3.07	2	0.83	0.10, 3.01
Other	19	0.97	0.58, 1.51	9	1.07	0.49, 2.03	10	0.89	0.43, 1.63
Colorectal cancer stage									
I and II	13	1.01	0.54, 1.72	5	0.84	0.27, 1.96	8	1.15	0.50, 2.27
III and IV	11	1.06	0.53, 1.89	7	1.52	0.61, 3.12	4	0.69	0.19, 1.76
Unknown									

* Basal cell carcinoma patients derived from patients diagnosed in 1990–2002.

risk of breast cancer compared with the general female population in southern Netherlands (SIR = 1.87, 95 percent CI: 1.14, 2.89).

When considering time since nonmelanoma skin cancer (SCC and BCC) diagnosis (table 5), we found that the relative risk of developing a subsequent colorectal or breast cancer slowly increased with time and was lowest during the early years after skin cancer diagnosis. Within the first year of skin cancer diagnosis, the risk of colorectal cancer was 30 percent lower than that of the general population (SIR = 0.71, 95 percent CI: 0.49, 0.99). After 4 years, the risk became similar to that of the general population. For

TABLE 3. Primary colon and rectal cancer among southern Netherlands patients with skin cancer diagnosed between 1972 and 2002* and followed until 2004, according to gender

Site of second cancer	Squamous cell carcinoma			Basal cell carcinoma			Cutaneous melanoma			All skin cancers		
	No. of cases	Standardized incidence ratio	95% confidence interval	No. of cases	Standardized incidence ratio	95% confidence interval	No. of cases	Standardized incidence ratio	95% confidence interval	No. of cases	Standardized incidence ratio	95% confidence interval
Colon	26	0.64	0.42, 0.94	147	0.93	0.79, 1.09	18	1.11	0.66, 1.76	191	0.89	0.77, 1.03
Male	18	0.66	0.39, 1.04	81	0.93	0.74, 1.16	7	1.02	0.41, 2.11	106	0.87	0.71, 1.06
Female	8	0.61	0.27, 1.21	66	0.93	0.72, 1.19	11	1.18	0.59, 2.10	85	0.91	0.73, 1.13
Rectum	17	0.78	0.46, 1.25	77	0.93	0.73, 1.16	6	0.68	0.25, 1.47	100	0.88	0.71, 1.07
Male	10	0.61	0.29, 1.13	41	0.78	0.56, 1.06	5	1.13	0.37, 2.64	56	0.77	0.58, 1.00
Female	7	1.28	0.51, 2.63	36	1.17	0.82, 1.63	1	0.22	0.01, 1.25	44	1.08	0.79, 1.46

* Basal cell carcinoma patients derived from patients diagnosed in 1990–2002.

TABLE 4. Primary female breast cancer among southern Netherlands patients with skin cancer diagnosed between 1972 and 2002* and followed until 2004

	No. of cases	Standardized incidence ratio	95% confidence interval
All skin cancers	236	1.01	0.88, 1.14
Squamous cell carcinoma	22	0.87	0.54, 1.31
Basal cell carcinoma	174	0.99	0.85, 1.15
Cutaneous melanoma	40	1.19	0.85, 1.63
Squamous cell carcinoma			
Age at diagnosis			
<60 years	8	1.98	0.85, 3.89
≥60 years	14	0.66	0.36, 1.10
Location			
Head and neck	13	0.79	0.42, 1.35
Other	8	0.92	0.40, 1.81
Breast cancer stage			
I and II	16	0.86	0.49, 1.40
III and IV	5	0.97	0.31, 2.27
Unknown	1	0.60	0.02, 3.32
Basal cell carcinoma			
Age at diagnosis			
<60 years	60	1.01	0.77, 1.30
≥60 years	114	0.98	0.81, 1.18
Location			
Head and neck	124	0.95	0.79, 1.13
Other	50	1.12	0.83, 1.48
Breast cancer stage			
I and II	154	1.09	0.92, 1.27
III and IV	15	0.53	0.30, 0.88
Unknown	5	0.83	0.27, 1.94
Cutaneous melanoma			
Age at diagnosis			
<60 years	20	0.88	0.53, 1.35
≥60 years	20	1.87	1.14, 2.89
Location			
Head and neck	6	1.38	0.50, 2.99
Other	34	1.18	0.82, 1.65
Breast cancer stage			
I and II	26	0.94	0.62, 1.38
III and IV	11	2.20	1.10, 3.94
Unknown			

* Basal cell carcinoma patients derived from patients diagnosed in 1990–2002.

CMM patients, we found a 40 percent lower risk of colorectal cancer compared with that of the general population during the first 2 years after diagnosis, followed by an increased risk in later years, but these results were not significant (data not shown). For breast cancer, we observed a significantly increased standardized incidence ratio during

TABLE 5. Relative risk of second colorectal or female breast cancer among southern Netherlands patients following nonmelanoma skin cancer diagnosed between 1972 and 2002 according to time since skin cancer diagnosis

Time since skin cancer diagnosis	Site of second primary cancer					
	Colorectum			Female breast		
	No. of cases	Standardized incidence ratio	95% confidence interval	No. of cases	Standardized incidence ratio	95% confidence interval
0–<1 year	35	0.71	0.49, 0.99	31	0.95	0.65, 1.36
1–<2 years	37	0.78	0.55, 1.08	26	0.83	0.54, 1.21
2–<3 years	33	0.78	0.53, 1.10	28	0.98	0.65, 1.42
3–<4 years	32	0.90	0.62, 1.28	24	1.00	0.64, 1.49
4–<5 years	34	1.14	0.79, 1.60	22	1.09	0.68, 1.65
≥5 years	96	0.97	0.79, 1.19	65	1.01	0.78, 1.29

the first year after diagnosis of CMM (10 breast cancer cases: SIR = 2.62, 95 percent CI: 1.25, 4.81).

In our skin cancer cohorts, 361 patients developed lung cancer (86, 263, and 12 in SCC, BCC, and CMM patients, respectively) (data not shown). We observed an increased risk of lung cancer after SCC (SIR = 1.21, 95 percent CI: 0.97, 1.49), a decreased risk for CMM patients (SIR = 0.47, 95 percent CI: 0.24, 0.84), and a risk similar to that of the general population for BCC patients (SIR = 1.09, 95 percent CI: 0.96, 1.23) compared with the general population.

DISCUSSION

In this large, population-based study of nearly 27,000 skin cancer patients, we found a decreased relative risk of colorectal cancer, especially for men. It was most apparent among those diagnosed with SSC, with a 19–36 percent lower risk of colorectal cancer for women and men compared with the risk for the general population. Older patients with SCC and patients with a lesion on the head and neck area also exhibited a reduced risk of colorectal cancer compared with that for the general population. Another novel result is the increasing risk over time after nonmelanoma skin cancer diagnosis, with the lowest relative risk in the early years. For women with a previous CMM at ages 60 or older, we observed almost a twofold increased risk of breast cancer. This increased risk was most marked for advanced stage breast cancer among female CMM patients.

The beneficial influence of sun exposure on cancer is generally presumed to be through vitamin D (34). Sunlight increases the synthesis of pre-vitamin D and is considered the main source of circulating vitamin D levels in humans. However, vitamin D is also derived from diet and supplements, although the contribution of diet on the circulating vitamin D level is small (35). Active vitamin D regulates cell growth and differentiation by binding to vitamin D receptors on various tissues (35). Of the 12 studies investigating the risk of colorectal or breast cancer after skin cancer diagnosis included in our review, three studies demonstrated increased risks of colorectal (25, 26, 31) and three studies demonstrated increased risks of breast (26, 27, 33) cancers after skin cancer (figures 1 and 2). One observed a significantly reduced risk of rectal cancer in men (27). The pooled estimates for all standardized incidence ratios were larger than 1. However, the heterogeneity tests for analyses of standardized incidence ratios for colorectal cancer in male skin cancer patients and breast cancer in skin cancer patients were statistically significant, illustrating the difficulty in comparing these studies. Several factors may explain the different findings across the studies. First, many studies did not stratify according to gender; in our study, men seemed to exhibit a larger risk reduction than did women (20, 33). Second, effect modification by age influenced results, with those younger at their first cancer diagnosis showing higher risks of developing a second cancer (15, 19, 24). Third, the skin cancer subsite was not investigated separately; that is, patients with a lesion on the head and neck area had the highest risk reduction. Finally, the studies listed had a long follow-up period (36), and the protective effect was most pronounced in the early period (20, 27, 33). Thus, by including patients with longer follow-up, the risk may have been elevated back to that of the general population.

SCC has been related to cumulative sun exposure (9) and is more common in men, probably because of their history of outdoor labor and the fact that women often have longer (and more) hair than men, protecting their scalp better against the sun. This high sun exposure would explain the highest protective effect of sunlight on colorectal cancer found for this group of patients. Physical activity may have been a confounding factor, as more physical exercise lowers the risk of colorectal cancer (37) and is related to more sun exposure and therefore a higher skin cancer risk. As for BCC compared with SCC, BCC patients have been reported to have the lower lifetime accumulated ultraviolet exposure and, thus, also the weaker risk reduction in our study (38). Furthermore, the stronger beneficial effect of vitamin D was observed in the distal colon and the rectum (39, 40). Like those of others (41), our finding did not indicate a different association for rectal cancer, although the low number of cases restricted our conclusion.

After a diagnosis of skin cancer, our patients 60 years or older at SCC diagnosis with a lesion on the head and neck area had the lowest relative risk of breast cancer. Similar

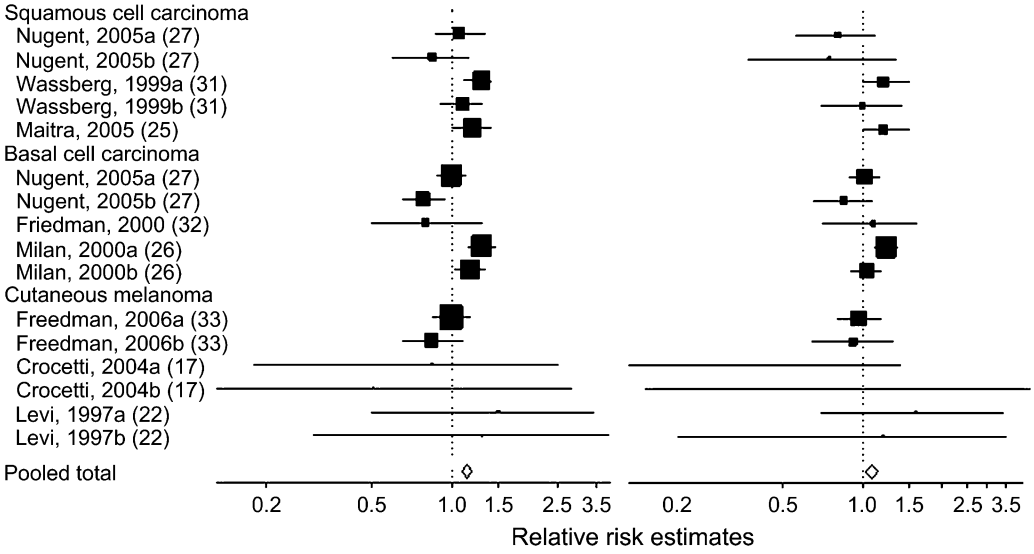

FIGURE 1. Studies on colorectal cancer risk after skin cancer, with results for males (left) and females (right). Pooled estimates for relative risk of colorectal cancer after skin cancer are 1.14 (95% confidence interval: 1.09, 1.19) for males and 1.08 (95% confidence interval: 1.03, 1.14) for females. Heterogeneity test: $p < 0.001$ for males and $p = 0.055$ for females. The numbers of cases from the studies by Crocetti et al. (17) and Levi et al. (22) were small and, thus, the point estimates were not apparent; "a" refers to estimates of colon cancer and "b" to those of rectal cancer.

reasoning to that for colorectal cancer may apply here: greater sun exposure for these patients. Moreover, when the risk was compared for SCC versus BCC versus CMM, an increasing trend was observed, which is in line with the amount of sun exposure among these cancer patients: highest for SCC and lowest for CMM patients (9). Previous studies reported an increased risk of breast cancer for CMM patients (19, 33). A reciprocal association was observed for women with breast cancer who have a higher risk of CMM (19, 42, 43). This may reflect a higher socioeconomic status, thus having more intermittent sun exposure (44) but also fewer children, older age at the first child's birth (45), and probably higher awareness of breast cancer leading to a higher screening attendance rate. This

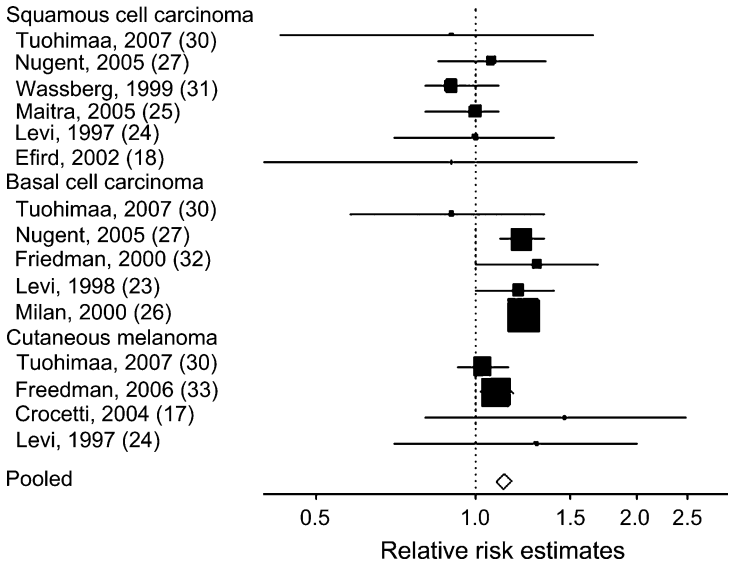

FIGURE 2. Studies on breast cancer risk after skin cancer. Pooled estimates for relative risk of breast cancer after skin cancer are 1.13 (95% confidence interval: 1.09, 1.17). Heterogeneity test: $p = 0.007$.

clustering of risk factors among the more advantaged may explain the relation between CMM and breast cancer. In addition, genetic predisposition to both CMM and breast cancer may have contributed to the elevated risk, although on a population level, this influence would have been minor (46, 47).

Vitamin D has been shown to delay cancer progression (34, 48). We found a lower risk of less advanced stage colorectal cancer for patients with SCC and BCC but not for patients with CMM. The risk of more advanced colorectal cancer was decreased among patients with SCC but not among patients with BCC and CMM. Chronic sun exposure seems to protect against any stage of colorectal cancer and, as the lifetime ultraviolet exposure becomes lower, as in the case of BCC patients, the protective effect is evident only for early colorectal cancer. In addition, we demonstrated a significantly decreased risk of advanced stage breast cancer for BCC patients. Yet, patients with CMM experienced a higher risk of advanced breast cancer. Genetic predisposition to both CMM and breast cancer may partly explain this finding (e.g., *BRCA2* mutation). Mutation carriers have been shown to have a higher grade of breast cancer compared with those without (49). An increased standardized incidence ratio of breast cancer was also found for elderly CMM patients, usually contrary to genetic-related cancer. However, the breast cancer risk for *BRCA2* carriers has been reported to persist even after menopause (49).

The strength of this study is its population-based nature, enabling comparisons with the same population from which the cases were obtained and avoiding selection bias of the control group. A population-based study also provides larger numbers for statistical analyses even after categorization of the factors studied. In addition, our registry is unique in that it systematically collected data on various skin cancer types, allowing us to compare the risk of second cancers among these groups with different sun exposure patterns.

Limitations of our study include the lack of individual breast or colorectal cancer risk factor data such as reproductive factors, external hormone or supplement intake, dietary information, and physical activity level. Skin cancer was taken as a proxy for higher sun exposure, and no information on actual sun exposure or other modifying factors such as skin type was available. Our findings may also be a result of chance. However, we have statistically tested the results illustrating the extent to which chance findings may have occurred. Furthermore, there is a plausible biologic explanation on the beneficial role of vitamin D on cancer risk (35). Further, methodological artifact seems to be an unlikely explanation because additional analyses showed an increased risk of lung cancer for SCC patients and a lower risk for CMM patients than we had hypothesized. The low relative risk of colorectal cancer during the early period after skin cancer diagnosis may be associated with endoscopy. Conversely, increased risk of breast cancer after melanoma may be a consequence of mammographic screening. However, in the Netherlands, voluntary screening for colorectal cancer is and has been very low, and no national colorectal screening program exists. The national breast cancer screening program has a relatively high coverage, but any effects of screening would not be expected to vary with time since skin diagnosis. Finally, the registration of basal cell carcinoma may not be as complete as those of the other skin malignancies. However, it is highly unlikely that underreporting is related to the risk of breast or colorectal cancer.

In conclusion, we have reported a lower risk of colorectal cancer in male skin cancer patients as compared with the general population, especially among those who are most chronically exposed to the sun, probably the result of sun-induced high levels of vitamin D. The beneficial influence of sun exposure in women was less evident, probably because it was diluted by other factors that might have increased the risk of skin as well as colorectal or breast cancer. Studies are needed to clarify the benefit of sun exposure and supplementation of vitamin D in preventing (as well as reducing) the progression of colorectal as well as breast cancer, so that public health measures and chemoprevention strategies can be adapted accordingly.

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