Merkel Cell Carcinoma and Melanoma: Etiological Similarities and Differences

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Abstract

Merkel cell carcinoma (MCC) of the skin and cutaneous malignant melanoma can now be compared epidemiologically through the use of population-based data not previously available for MCC. The results may provide new clues to etiology. In this study, United States data covered by the Surveillance, Epidemiology, and End Results (SEER) Program were from nine areas of the United States (~10% of the population). In 1986–1994, 425 cases of MCC were registered. The annual age-adjusted incidence per 100,000 of MCC was 0.23 for whites and 0.01 for blacks; among whites, the ratio of melanoma to MCC was ~65 to 1. Only 5% of MCC occurred before age 50, unlike the lifelong risk of nodular and superficial spreading melanoma. Regional incidence rates of both cancers increased similarly with increasing sun exposure as measured by the UVB solar index. The most sun-exposed anatomical site, the face, was the location of 36% of MCC but only 14% of melanoma. Both cancers increased in frequency and aggressiveness after immunosuppression and organ transplantation (36 cases from the Cincinnati Tranplant Tumor registry and 12 from published case reports) and after B-cell neoplasia (5 cases in this study; 13 from case series in the literature). The SEER data contained reports of six patients with both types of cancer; 5 melanomas before the diagnosis of MCC and 1 after diagnosis. MCC and melanoma are similarly related to sun exposure and immunosuppression, but they differ markedly from one another in their distributions by age, race, and anatomical site, especially the face.

Introduction

In 1875, Merkel described cells of the skin that now bear his name. Carcinoma thought to be of these cells was first reported in 1978 (1), and hundreds of cases have since been described. MCC[2] and cutaneous malignant melanoma have similar clinical courses. Neural crest derivation is known for melanoma and suspected for MCC (2). In 1986, the diagnosis of MCC was added to the list of cancers registered by the population-based SEER Program of the National Cancer Institute. These data were compared with those for melanoma and examined for epidemiological clues to etiology.

Materials and Methods

Incidence data were from the SEER Program, January 1, 1986, through December 31, 1994. At that time, the SEER Program collected data on the incidence of cancer in five states (Connecticut, Utah, New Mexico, Iowa, and Hawaii), and four metropolitan areas (Detroit SMSA, San Francisco-Oakland SMSA, Atlanta SMSA, and Seattle-Puget Sound; Ref. 3). This population-based registry covered about 10% of the United States population. As is usual for the SEER Program, histological specimens (for all of MCC and 99.5% of melanoma) were examined at the time and place of diagnosis. The search for second primary cancers extended back to the beginning of the registry in 1973. Reviews of the literature were the source of data on case reports of MCC and melanoma after organ transplantation or B cell cancers.

The solar UVB index (the estimated annual exposure to solar UVB radiation, on a relative erythema induction scale for people in each registry area) was the same as that used by Scotto *et al.* (4), with the additional estimated value of 265 for Hawaii provided by these authors.[3] The association between MCC incidence and solar UVB was evaluated by the χ^2 test for trend (Epicure statistical package, HiroSoft International Corp., Seattle, WA).

Subjects with cancers registered by SEER are uniquely identified, so more than one cancer can be recorded for the same individual as long as he or she lives in a SEER area. All persons with cancer were followed annually to determine vital status. The various tracing methods have been described by Ries *et al.* (5). We identified persons who had MCC and some other cancer, and, for cancers that were possibly in excess, we determined the person-years at risk of subsequent MCC after NHL, CLL, and melanoma (from the date of first cancer diagnosis to the date of death or last follow-up). The analyses of multiple cancers covered first and subsequent primary cancers through December 31, 1993. The subsequent primary tumors were of different histological classification. Observed frequencies were compared with expected numbers based on age-, sex-, and calendar year-specific incidence rates and the accumulated person-years at risk. Exact 95% CIs for relative risk estimates (i.e, the ratio of observed incidence to expected incidence) were computed from a table of the Poisson distribution (6).

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[2] The abbreviations used are: MCC, Merkel cell carcinoma; SEER, Surveillance, Epidemiology and End Results; NHL, non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; MM, multiple myeloma; XP, xeroderma pigmentosum; SMSA, standard metropolitan statistical area; CI, confidence interval.

[3] T. R. Fears, personal communication.

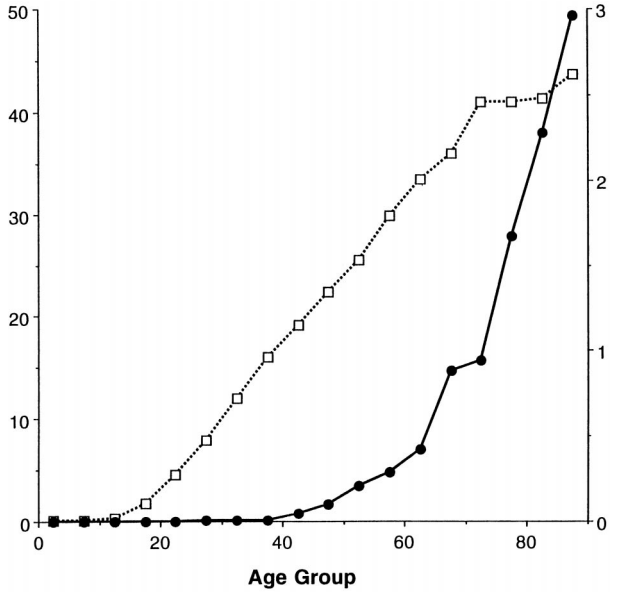

Fig. 1. Incidence of cutaneous melanoma (□) and MCC (●) of skin by age. Data are from whites in the SEER Program, 1986–1994.

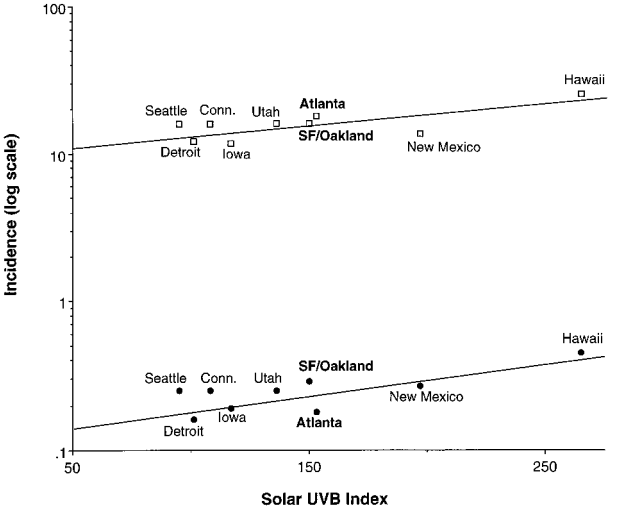

Fig. 2. Incidence in United States whites of MCC (●) and melanoma (□) by UVB index. Data are from nine SEER registries, 1986–1994.

Results

In the 9-year interval, 1986–1994, the SEER Program registered 425 persons with MCC and 27,893 with cutaneous melanoma. These numbers in ~10% of the population covered by SEER translate into about 470 new cases of MCC and 31,000 of melanoma in the United States annually. Among the 414 MCC with race specified, 97.1% were white. Only 2 were black, as compared with 32 cases expected ($P < 0.001$; relative risk, 0.06; 95% CI, 0.02–0.24) based on the frequency (7.7%) of blacks over age 50 in the SEER Program. Among the 27,893 with melanoma, only 0.5% were black, well below their frequency (10.8%, all ages) in the SEER Program.

In whites, the age-adjusted annual incidence of MCC was 0.35 per 100,000 in males and 0.15 in females. The corresponding incidence of melanoma per year was 17.9 in males and 12.9 in females. The rate for MCC increased rapidly beginning at age 50, very different from the much earlier rise for melanoma (Fig. 1). Fig. 2 shows that the incidence of MCC and melanoma rose as potential exposure to solar UVB increased with respect to the various geographic areas covered by the SEER Registry (MCC: $P = 0.006$; $r^2 = 68\%$ for the log rate *versus* solar UVB weighted by the number of cases). On average, the logarithms of the incidence rate for MCC increased by 0.0021 for each unit of increase in the solar UVB index, which is similar to the increase for melanoma of 0.0016. The rates were highly correlated except for Atlanta, where the MCC incidence was an outlier (low).

The face, in particular, was affected in MCC (36% of cases) but not in melanoma (14% of cases; Table 1). The percentages of the most common sites of melanoma were 43% for the trunks of males and 34% for the legs of females. In the SEER Registry for Hawaii, MCC was reported in five Hawaiians, all with MCC of the extremities, three Japanese-Americans, all with the face affected, and eight whites, four of whom had MCC of the face. No cases were reported among Chinese, Koreans, Filipinos, Vietnamese, Hispanics, or blacks, whose population over age 55, in the aggregate, outnumbered the Hawaiians by 2 to 1.

Through the SEER Registry, we found eight cases of MCC with CLL or NHL (Table 2). Five preceded MCC, one was simultaneous, and two occurred 5 and 50 months after MCC. All five NHL histological diagnoses were of subtypes that are almost always due to B-cell neoplasia (7).

Five melanomas were reported before diagnosis of MCC, and one 10 months after (Table 2). Three subtypes occurred among the four with subtypes specified. In each of the six cases, the two neoplasms were at different anatomical sites. The observed/expected ratio for the occurrence of melanoma before MCC was 5.2 (95% CI, 1.7–12.1). Reports were found in the literature for 19 persons with MCC who had preexisting B-cell cancers (Table 3). All but four were from hospital case series. The interval between cancers was 3.5–6 years for the four cases for whom this information was reported.

Review of the literature revealed that 12 cases of MCC developed after immunosuppressive therapy and organ transplantation (Table 4). Another 36 have been found in the Cincinnati Transplant Tumor Registry.[4] In the 12 case reports, the onset of cancer was in 5 years or less, except for one case that occurred 15 years later. Time until death was known for six cases, four of whom died within 11 months; the other two died 2 years after the diagnosis of MCC.

Discussion

In a recent molecular study, Vortmeyer *et al.* (2) found that among 10 MCC, 7 showed deletions involving chromosome 1p35–36, the same location has been suspected for genetic changes in pheochromocytoma, neuroblastoma, and (arguably) melanoma. The authors concluded that Merkel cell carcinogenesis shares pathogenetic mechanisms with other neoplasms of neural crest derivation.

Table 5 summarizes similarities and differences between MCC and melanoma. The rise in incidence of MCC with the solar UVB index proved to be almost identical to that for melanoma. Skin pigmentation has been thought to protect blacks and Japanese against melanoma. SEER data show that

[4] E. G. Silva, personal communication.

Table 1 Anatomic distribution (percentage) of MCC and melanoma in United States whites, SEER Program, 1986–1994

Site	MCC			Melanoma		
	Male	Female	Total	Male	Female	Total
Total face	39.5	30.1	35.5	17.0	10.2	13.9
Lip	4.9	3.3	4.1	0.2	0.2	0.2
Eyelid	0.8	0.7	0.8	0.4	0.4	0.4
Ear	8.0	1.3	5.2	5.1	0.8	3.1
Other face	25.8	24.8	25.4	11.3	8.8	10.2
Scalp/neck	9.9	10.5	10.1	8.2	4.1	6.3
Arm/shoulder	21.1	20.3	20.8	21.5	26.0	23.5
Trunk	16.0	17.6	16.7	43.2	26.2	35.7
Leg/hip	13.6	21.6	16.9	9.4	33.5	20.5
Age-adjusted rate[a]	0.35	0.15	0.23	17.87	12.90	14.9

[a] Per 100,000 per year.

Table 2 MCC with NHL, CLL, or melanoma, SEER Registry, 1986–1994

Case no.	Sex	Age		Interval	Other cancer		MCC site
		Other cancer	MCC		Cell type	Site	
1	M	59	60	13 m	NHL, small cell cleaved diffuse	Lymph node	NFS[a]
2	F	69	77	8 yr	NHL, small cell lymphocytic	Lymph node	Upper limb
3	M	58	58	2 m	NHL, large cell diffuse	Anterior mediastinum	Ear
4	M	72	72	0 m	NHL, small cell cleaved diffuse	Lymph node	Face
5	F	88	84	−50m[b]	NHL, lymphoplasmocytic	Lymph node	Lower limb
6	M	68	73	65 m	CLL		Lower limb
7	F	65	68	34 m	CLL		Upper limb
8	M	80	80	−5m[b]	CLL		Lower limb
9	M	73	84	133 m	Melanoma, spindle cell	Scalp	Ear
10	M	68	77	107 m	Melanoma, NFS	Trunk	Scalp
11	M	74	80	71 m	Melanoma, spreading	Face	Leg
12	F	71	75	51 m	Melanoma, NFS	Face	Leg
13	M	88	91	32 m	Melanoma, nodular	Ear	Scalp
14	M	77	76	−10m[b]	Melanoma, spreading	Arm	Scalp

[a] NFS, not further specified.
[b] MCC was the initial cancer.

MCC rarely develops in blacks, but the susceptibility of Japanese is indicated by their high relative frequency of MCC of the face, 74% of 99 cases. Thirty-two of these reports were from a review of the Japanese literature through 1989 (24), and, for 1990–1997, 67 were found by Ishikawa[5] through the use of Igaku-Chuo-Zasshi, a computer index to Japanese-language medical publications. Another clue to the prevalence of MCC in Japan is from an abstract by Kayashima (25), who reported that 174 cases were ascertained by a survey of certain academic departments of ophthalmology and dermatology through 1995. Probably, there is considerable overlap in the two sources of information. In any event, it appears that MCC is not so rare among Japanese as among blacks, and the high percentage affecting the face suggests sun induction.

Fitzpatrick (26) was one of the first to question the belief that skin pigmentation protects blacks against melanoma. He noted that black albinos in Africa, deprived of their pigmentation, rarely develop melanoma. Reports concerning almost 1000 albinos in Tanzania (27, 28), South Africa (29), and Cameroon (30) indicated that by far the most frequent skin cancer was squamous cell carcinoma early in life. Each African group had only a few basal cell carcinomas, and only one melanoma was reported in this sample (27), which indicates, as noted by Weinstock (31), that if there is an increase in melanoma, it is not by an order of magnitude as in XP (see below). (Among all races, only 27 melanomas have been reported in albinos [32–34]. These reviews of the literature listed a total of 4 African blacks, 1 American black (34), 4 Japanese, and 18 whites.) In whites with familial melanoma and mutations of CDKN2A (which encodes the protein p16), the lesser the skin pigmentation, the greater was the risk of melanoma. (35). Thus, depth of skin pigmentation as protection against melanoma may apply only to whites.

The estimated annual incidence of melanoma in native Japanese is 0.33 per 100,000, half of it due to the acral lentiginous subtype (36), which has the same rate in all races and is not related to sun exposure (36, 37). The low rate of melanoma in Japanese may be due not to protection against UV by their skin pigmentation but to the influence that accounts as well for the low frequency of dysplastic nevi in Japanese (38, 39). These nevi are markers of increased risk or precursors of melanoma (40–42). Notably, the Japanese literature through 1989 contained only two reports of dysplastic nevus syndrome with familial melanoma (38, 39). Despite their much lighter skin pigmentation, they have a lower melanoma incidence rate than

[5] Y. Ishikawa, personal communication.

Table 3 MCC after B-cell malignancies, from the literature and the SEER Program

No. MCC in series	CLL	NHL	MM	Interval, diagnosis to death	References
93[a]	3	2	1		Silva *et al.* (8)
					Eftekhari *et al.* (9)
3	2			−4 yr[b]	Kuhajda *et al.* (10)
1	1			−3.5 yr	Safidi *et al.* (11)
1	1				Quaglino *et al.* (12)
27	2				Brenner *et al.* (13)
50		1		−6 yr	Pilotti *et al.* (14)
34	2[c]		2[d]		Boyle *et al.* (15)
425	2[e]	4[f]		—[g]	Present study
Total	13	7	3		

[a] M. D. Anderson series 1984 and 1996.
[b] Same interval for both cases of CLL.
[c] Deaths in 3 and 21 months.
[d] Deaths in 10 months of another disease and in 34 months, no evidence of MCC.
[e] Excludes one case of CLL 5 months after diagnosis of MCC.
[f] One simultaneous diagnosis of MCC and NHL; see Table 2.
[g] See Table 2 for intervals to MCC.

Table 4 MCC in organ transplant recipients, from the literature[a]

Case no.	Reference	Age	Sex	Site	Onset	Metastasis	Death	Transplant
1	Dantal *et al.* (16)	65	M	Leg	21 m	Yes	10 m	Kidney
2	Dantal *et al.* (16)	65	M	Arm	2 yr			Kidney
3	Dantal *et al.* (16)	48	M	Face	4 m	Yes	4 m	Kidney
4	Dantal *et al.* (16)	17	F	Scalp	5 yr	Yes	7 m	Kidney
5	Formica *et al.* (17)	54	M	Chest	3 yr	1 yr		Kidney
6	Douds *et al.* (18)	67	M	Thigh	2 yr	2 yr	2 yr	Kidney
7	Gooptu *et al.* (19)	56	F	Leg	4 yr	Same		Kidney/liver
8	Gooptu *et al.* (19)	55	M	Neck	15 yr	Soon	6 m	Kidney
9	Williams *et al.* (20)	65	M					Kidney
10	Stempfle *et al.* (21)	51	F	Arm	0 m	5 m		Heart
11	Pham *et al.* (22)	55	M	Nose	5 yr		2.3 yr	Heart
12	Veness (23)	54	M	Scalp	3 yr	21 m		Heart

[a] Unpublished data concerning cases 1–4 and 11 were provided by the authors (J. Dantal, personal communication; S. M. Pham, personal communication). An additional 36 cases have been found among 4269 skin cancers in the Cincinnati Transplant Tumor Registry.

do United States blacks (0.33 *versus* 0.89, respectively, per 100,000 per year). To our knowledge, the number of dysplastic nevi in blacks has not been surveyed, so the possibility exists that they too have low susceptibility to melanoma, apart from skin pigmentation.

Review of the literature yielded reports since 1993 of MCC in 12 persons after immunosuppression for organ transplantation. In addition, among 4269 skin cancers recorded in the Cincinnati Transplant Tumor Registry, 36 were MCC.[6] The registry now contains about 220 melanomas (5.2% of all skin cancers [43]), so the ratio of posttransplant melanoma to MCC is 6 to 1, as compared to 65 to 1 in the general population. This observation suggests that in transplant recipients, the threshold for developing MCC is reduced more than that for melanoma. Part of this difference may be attributable to fuller ascertainment of MCC in transplant recipients, related to their close scrutiny for skin cancer, and the use of the special tests to separate MCC from morphologically similar neoplasms (44).

Penn (43) has observed that the anatomical distribution of 164 posttransplant melanomas was the same as in the general population, indicating an interaction that enhances the effect of the usual etiological factors. In accord with the foregoing are data from the World Wide Web site for the Collaborative Transplant Study,[7] which show that after transplantation of 88,350 kidneys, the cumulative incidence of skin cancer 6 years after implant was more than 5 times greater in Australia than in the United States and Europe.

There is a marked excess of melanoma in XP, estimated to be more than 1000 times the normal rate in persons under age 20 years (45). The head and neck was affected in 65% of cases in a review of the literature, 1874–1982 (46), and in 34% of cases reported to the XP Registry since 1980 (45). In the general population, the head and neck accounted for only 20% of melanoma, well below the percentages for the commonest sites of melanoma, the trunks of males (43%) and the legs of females (34%). The high frequency in persons with XP indicates that the defective DNA repair vastly outweighs whatever protects against melanoma in the general population. MCC has not been reported in XP. About 10 cases would be expected if the ratio of melanoma to MCC were 6 to 1, as in transplant recipients.

In psoriasis, after treatment with psoralin and UVA radiation, three patients have been reported with MCC. Excesses of melanoma and nonmelanoma skin cancers have previously been reported (47).

[6] I. Penn, personal communication.

[7] G. Opelz, Collaborative Transplant Study Newsletter, February 20, 1997, http://www.ukl.uni-heidelberg.de/immu/newsletter/1997/1997-1.html.

Table 5 Findings in MCC as compared with melanoma

	MCC	Melanoma
Neural crest origin	Suspected	Yes
Age	95% over 50 yr	Occurs at all ages
Sun-inducible	Incidence rises with solar UVB index	Similar rise
Anatomic sites	Commonest on face	Seldom on face[a] Commonest on male, trunks; female, legs
Fraction on face	36% in whites, 74% in Japanese	14% in whites, 16% in Japanese
Albinos	Too rare; no cases reported	Increased frequency in whites not markedly different from blacks
In XP	No cases reported	1000-fold excess, 34–65% on face
After organ transplant	Rate rises, shortened survival	Rate rises, shortened survival
After B-cell neoplasia	Rate rises	Rate rises

[a] About half of facial melanomas are of the lentigo maligna subtype, which occurs after age 50 and is related to sun exposure (SEER Registry).

As noted above, 74% of MCC in native Japanese was of the face. MCC did not occur on the scalp or the neck. Seventy-two of the 99 cases with MCC were female, mostly over 70 years of age. Information on occupation is not available, but it seems likely that these women spent long hours as field workers during and just after World War II, before mechanized farming was introduced. They avoided the sun by wearing clothes that covered them from head to foot, including a wrap around their heads and necks so only their faces were exposed. Their exposures to the sun might thus be similar to those of patients with XP and would account for their high percentage of facial MCC but none on the scalp or neck. In a series of 480 Japanese with melanoma excluding the acral lentiginous type, the frequency of primaries of the face was 16% (48), similar to that in whites. It appears, then, that skin pigmentation did not protect Japanese against MCC, as it may protect blacks (only 2 among our 425 cases, and 1 among 93 cases at M. D. Anderson Cancer Center [9]).

The occurrence of B-cell neoplasms before MCC has been described since 1984. In large series, of MCC about 5% of cases were preceded by NHL, CLL, or MM (8, 9, 13–15). At this frequency, we expected about 20 cases in our series of 425 MCC. The five cases actually found in the SEER Program were well below the anticipated increase. Subclinical immunological changes due to the lymphoid neoplasms may have affected an additional person who had simultaneous tumors and two more whose MCC preceded the lymphoid neoplasm by 5 and 50 months. Our series fell short of demonstrating the expected excess, but when taken together with those in the literature, there is no doubt that these immunosuppressive neoplasms increase the risk of MCC. The literature disclosed that five MMs were diagnosed before MCC (8, 15), but there were none in the SEER series. More well-documented reports are needed to establish an association with MCC.

Large-scale population-based record-linkage studies have shown that NHL and CLL have been followed by 2–3 times the expected numbers of melanoma (49–51). Thus, both melanoma and MCC occur excessively after these B-cell neoplasms or after immunosuppressive therapy for organ transplantation. Also, in a study of 906 men discharged from Veterans Affairs hospitals with a diagnosis of Felty syndrome (severe rheumatoid arthritis, neutropenia and recurrent infections) had a 12-fold excess of NHL and a 7-fold excess of melanoma (52). This is another instance in which both these neoplasms occur excessively in a disease with immunological disorders.

Immunosuppression from HIV infection has not been related to MCC. Only one case has been described (53). The risk may be lower because of young age (7) and their (former) short life spans. Published case reports raised the possibility that AIDS increased the risk of melanoma (reviewed by Weinstock [31]), but only a small excess was found in a mortality study of persons with the infection (54).

The occurrence of 6 melanomas among 425 people with MCC in the SEER series was unexpected. All but one were diagnosed 3–11 years before the occurrence of MCC at ages 75–91. The accuracy of diagnosis comes into question: were these double primaries of dissimilar cell type or a misdiagnosed recurrence of the same neoplasm? The dissimilar anatomical sites of the two neoplasms in each case may favor the belief that they were separate tumors. In a report from M. D. Anderson Cancer Center, two cases with MCC and melanoma were mentioned (9), and inquiry to one of the authors[8] revealed that in at least one case, the tumors met the stringent criteria for diagnosing these separate neoplasms (44). Additional case reports are needed to establish that the seeming excess is not attributable to misdiagnosis.

Squamous cell carcinoma is also thought to occur excessively in persons with MCC (55), an association not evaluable here because SEER does not register skin cancers other than melanoma and MCC. It is, of course, biologically plausible that all three skin cancers in excess after organ transplantation would occur excessively together in patients without organ transplantation. In contrast to other skin cancers, an excess of MCC has not been reported in XP because of its low frequency and/or a mechanism that involves a DNA repair defect rather than immunosuppression.

The descriptive epidemiology of these tumors reveals peculiarities in their occurrence by anatomical site, race, and associated diseases. Further understanding of the reasons for these patterns and associations should be sought to advance our knowledge of the origins of both MCC and melanoma.

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