Epidemiology of primary Merkel cell carcinoma in the United States

Maria Agelli, MD, MS,[a] and Limin X. Clegg, PhD, MS[b]
Bethesda, Maryland

Background: Merkel cell carcinoma (MCC) is a rare, aggressive skin cancer.

Objective: We sought to describe primary MCC incidence trends, epidemiology, and predictors of survival.

Methods: The population covered by the Surveillance, Epidemiology, and End Results Program was analyzed as a prospective cohort. We measured age-adjusted incidence rates (per 100,000 person-years) and effect of age, anatomic site, and stage on survival.

Results: Incidence was higher in males (0.34) than in females (0.17). Cases (n = 1034) occurred mostly in whites (94%), in people older than 65 years (76%), and at the head (48%). The 5-year relative survival was 75%, 59%, and 25% for localized, regional, and distant MCC, respectively. Female sex, limb presentation, localized disease, and younger age were positive predictors of survival.

Conclusion: The highest incidence of MCC was observed in whites, males, and in people older than 65 years. Only 49% of cases were reported as localized. Better survival was associated with limb localization, early-stage disease, younger age, and female sex. (J Am Acad Dermatol 2003;49:832-41.)

Merkel cell carcinoma (MCC) is a rare, aggressive skin cancer that occurs most frequently in the elderly on sun-exposed skin; however, any possible cutaneous or mucosal site may be involved.[1,2] MCC usually presents as a rapidly growing, painless, single red or purple cutaneous nodule or indurated plaque that will elude diagnosis until histopathologic examination.[2-10] MCC is characterized by a high incidence of local recurrence, regional nodal metastasis, distant metastasis, and a high mortality rate.[2-10] Several treatment modalities have been proposed,[1-3,5,6,8,11-13] but, because of the neoplasm's rarity and the absence of clinical trials, none have been proven to improve survival.[2] Infrequent spontaneous regression has been reported.[2,14,15]

MCC was first described by Toker[16] in 1972 as trabecular carcinoma of the skin because of its histologic appearance. In 1978, ultrastructural studies detected dense-core granules located in the cytoplasm at the periphery of the tumor cells.[17] Merkel cells,[2,6,18] identified in 1875 by Friedrich Sigmund Merkel in the basal layer of the epidermis associated with nerve endings,[19] are the only cells in the skin known to contain these kinds of granules. Therefore, the authors proposed that trabecular cell carcinoma of the skin derived from Merkel cells. (Neurosecretory) granules, similar to those seen in Merkel cells, have also been described in tumors of neuroendocrine origin. For this reason, MCC has been frequently reported as cutaneous neuroendocrine carcinoma.[10,20-22] In 1980, the name "Merkel cell carcinoma" was proposed[23] and, because of the confirmed ultrastructural similarity of these neoplastic cells with Merkel cells,[20,23] the name became prevalent.

Abbreviations used:

CI:	confidence interval
HR:	hazard ratio
MCC:	Merkel cell carcinoma
NCI:	National Cancer Institute
SEER:	Surveillance, Epidemiology, and End Results
UVB:	ultraviolet B

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Reprint requests: Maria Agelli, MD, MS, National Cancer Institute/OCTR, 6116 Executive Blvd, Suite 7021, Bethesda, MD 20892-8346. E-mail: ma215e@nih.gov.
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Information about the natural history, epidemiology, and clinical features of MCC are scarce because studies have been hampered by the difficult differential diagnosis with other primary and metastatic skin lesions,[2-10,24] its unknown origin,[2,6] multiple names,[7,25,26] and rare occurrence. The diagnosis of MCC was facilitated, and sometimes made possible,[1,10] when electron microscopy[17,20,24] and immunohistochemical staining for neuron-specific enolase,[27-29] other markers,[30] and cytokeratin 20[31-33] were introduced and became widely used. Three studies, including 1 based on the population followed by the Surveillance, Epidemiology, and End Results (SEER) Program,[34] reported MCC incidence in different populations.[4,34,35] However, what is known about MCC derives almost exclusively from case series and literature reviews that compiled previously published case reports.[2-11,13,20,36,37] Epidemiologic and survival data are still incomplete or inconsistent.

The goal of this study was to fill these gaps and, in particular, to ascertain primary MCC incidence trends, epidemiology, and predictors of survival in the 2 sexes. For this purpose, we analyzed first primary MCC reported to the SEER Program of the National Cancer Institute (NCI) by geographic areas covering 10% to 14% of the US population between 1973, just 1 year after the first description of this disease,[16] and 1999.

PATIENTS AND METHODS

SEER geographic areas

We used the incidence and survival data collected by the geographic areas participating in the SEER program of the NCI. The SEER Program began case ascertainment on January 1, 1973, with the cancer registries of the states of Connecticut, Iowa, New Mexico, Utah, and Hawaii and the metropolitan areas of Detroit, Michigan, and San Francisco-Oakland, California.[38] In 1974 and 1975, the Puget Sound area of Seattle, Washington, and the metropolitan area of Atlanta, Georgia, were added to the SEER Program. Henceforth, these 9 geographic areas will be referred to as SEER-9. SEER-9 covers approximately 10% of the US population. In 1992, the metropolitan area of Los Angeles and the area of San Jose-Monterey, California, joined the SEER Program bringing the population covered to about 14% of the US population. Hereafter, these 11 geographic areas will be referred to as SEER-11. The demographic characteristics of the SEER population compared with the US population are described elsewhere.[38,39]

Baseline measurements

Geographic areas participating in the SEER Program routinely collect data on patient demographics, primary tumor site, morphology, stage at diagnosis, first course of treatment, and follow-up for vital status as described elsewhere.[38,39] The histologic code for trabecular carcinoma of the skin was included in the Manual of Tumor Nomenclature and Coding (used by SEER in 1973-1975)[40] and in the first edition of the *International Classification of Diseases for Oncology*.[40] SEER has been reporting it continuously since 1973. The histologic codes for cutaneous neuroendocrine carcinoma and MCC were added to first edition of the *International Classification of Diseases for Oncology* in 1986[25] and SEER has been reporting them since then. In this study, incident cases were identified using the second edition of the *International Classification of Diseases for Oncology*[26] morphology codes 8190 (trabecular carcinoma of the skin, n = 81), 8246 (cutaneous neuroendocrine carcinoma, n = 69), and 8267 (MCC, n = 884), and topographic codes for the skin of the whole body and mucosa of the mouth, pharynx, larynx, and genitalia. Henceforth, for the purpose of this study, the term "MCC" will include also tumors coded as trabecular carcinoma of the skin and as cutaneous neuroendocrine carcinoma.

Cases were categorized into 5 major anatomic sites according to site of presentation at time of diagnosis: head (any area of the face, neck, and scalp); trunk (any area of the chest, back, abdomen, buttocks, and genitalia); upper limb (shoulder, and any area of the arm, forearm, wrist, and hand); lower limb (hips, and any area of the thigh, leg, ankle, and foot); and other (tumors overlapping 2 or more anatomic sites). The staging system used by the SEER Program is similar to that generally accepted for MCC[37,41]: localized to the skin (stage I), regional lymph node involvement (stage II), and distant metastasis (stage III). Tumor size was available only for 50% of cases during the period 1988 to 1999; therefore, it was not used to subdivide stage I into IA and IB. The estimated annual solar UVB radiation indexes used here were those calculated by Scotto et al.[34,42]

Statistical methods

We analyzed females and males separately. Incidence and age-adjusted incidence rates, based on the year 2000 US standard population, were calculated for the SEER-9 geographic areas, because data for the Los Angeles and San Jose-Monterey areas were not available for the entire period covered in this study. All incidence rates were calculated with (SEER*Stat 4.2)[43] software (SEER Program, NCI) and expressed as cases per 100,000 person-years. Incidence by year of diagnosis and by age was calculated from 1973 to 1999. In all other instances, for

ready comparison with published literature,[34,35] incidence rates were calculated from 1986 to 1999. Observed and relative survivals of cases reported between 1973 and 1999 were calculated (SEER*Stat) for SEER-9 (1973-1991) and SEER-11 (1992-1999) geographic areas in yearly intervals using the life table method. The analysis of disease-specific survival was not possible because the term "MCC" is not indexed as mortality code in *International Classification of Diseases, Ninth Revision*; therefore, we analyzed relative survival. The relative survival rate is the ratio of the observed survival to the expected survival of the general population of the same age, sex, and race of the patient group, and calendar year of observation.[44] We used Cox proportional hazards regression analysis (PHREG, SAS, Version 8.2, SAS Institute Inc, Cary, NC) with follow-up time in months, to evaluate if age, tumor anatomic site, and stage at diagnosis were associated with observed survival in males and females separately. Furthermore, multivariate adjusted female to male hazard ratios (HRs) and 95% confidence intervals (CIs) were obtained with Cox regression analysis with baseline hazards stratified by age, anatomic site, and stage. Reference categories and dummy variables were created as follows: age <65 years (reference category); age 65 to 74 years, and age >75 years; stage at diagnosis: localized (reference category), regional, distant, and unstaged; anatomic site: upper limb (reference category), head, trunk, lower limb, and other. Upper limb was chosen as reference category because the results obtained with univariate analysis indicated that localization at the limbs was associated with earlier diagnosis. In addition, because of the large number of observations, "upper limb" is stable as a reference category. Age-adjusted incidence rates by anatomic site stratified by age and sex, and 5-year survival trends over time were not reported because of the small numbers of observations in the different categories. For all analyses, 2-sided tests were used with a nominal significance level of .05.

RESULTS

Of the 1375 cases of MCC identified between 1973 and 1999, 341 were excluded because they were secondary to other primary cancers (n = 318), the diagnosis was not confirmed microscopically (n = 5), or they had no reported follow-up (n = 18). Of the 1034 cases of primary MCC included in this study, 21 (2%) were reported from 1973 to 1982, 255 (24.7%) from 1983 to 1991, and 758 (73.3%) from 1992 to 1999. About 4.5% of cases involved mucosal anatomic sites (nasal cavity, n = 15; mouth, n = 5; pharynx, n = 9; larynx, n = 15; vagina, n = 3). The major characteristics of cases are shown in Table I.

More than 76% of cases were reported in individuals 65 years or older and almost 50% of all cases of primary MCC were reported in people older than 75 years (Table I). About 94% of cases occurred in whites. Primary MCC affected males at a younger age than females ($P < .0001$) (Table I). In males, the anatomic site most frequently affected varied with age ($P < .0001$). In particular, the proportion of cases at the head increased from 29.8% in males less than 65 years old to 50% and 54.7% in males 65-74 years old and more than 75 years old, respectively. Localization at the trunk and limbs was more frequent in males less than 65 years of age (Table I). In females, affected anatomic sites did not change significantly with advancing age ($P = 1.0$) (Table I). There was no association between stage at diagnosis and sex ($P = .95$) or between stage at diagnosis and age ($P = .6$) (data not shown). Stage at diagnosis differed with anatomic site of presentation in both sexes (males, $P < .0001$; females, $P < .0001$). Primary MCC of the trunk was most frequently diagnosed at stage III, especially in females, whereas primary MCC of the limbs was most often diagnosed at stage I or II (Table I).

The age-adjusted incidence rate of primary MCC (SEER-9) according to calendar year of diagnosis and sex is presented in Fig 1. During the first 10 years, only a few cases were reported. Thereafter, the incidence of primary MCC has been increasing in both sexes from 1983 (males, 0.15; females, 0.08) until 1996 (males, 0.50; females, 0.22), when it seems to have reached a plateau or begun a slight decline (Fig 1). In both sexes, the incidence of primary MCC increased with advancing age, gradually from age 50 to 65 years, then progressively (Fig 2 and Table II). Males had a higher incidence compared with females in all ethnic groups studied with a ratio of 2:1 in whites and in blacks, and a ratio of 1.5:1 in all other ethnic groups. Whites had the highest incidence among the ethnic groups studied (Table II). In whites, the incidence rate was 11.3 times higher than in blacks and 2.2 times higher than in all other ethnic groups. When all ethnic groups were analyzed together, there was no correlation between age-adjusted incidence of primary MCC and estimated UVB index of the different SEER geographic areas for all cases ($r = 0.02$; $P = 1.0$) or for cases of the head only ($r = 0.26$; $P = .5$) (data not shown). However, when we analyzed whites separately, the highest age-adjusted incidence was in Hawaii (0.29), the geographic location with the highest UVB index (265) and a significant correla-

Table I. Characteristics of the 1034 patients with first primary Merkel cell carcinoma as reported to the Surveillance, Epidemiology, and End Results Program (SEER 1973-1999)

	Males N = 582 (56.3%)		Females N = 452 (43.7%)		Total N = 1034	
Age (y)						
Median	73		76		74	
Mean*	70.9		74.1		72.3	
Range	8-98		24-101		8-101	
	No.	**(%)††**	**No.**	**(%)†**	**No.**	**(%)†**
Age groups (y)						
<65	158	(27.2)	89	(19.7)	247	(23.9)
65-74	170	(29.2)	111	(24.6)	281	(27.2)
≥75	254	(43.6)	252	(55.8)	506	(48.9)
Race						
White	541	(93.0)	427	(94.5)	968	(93.6)
Black	8	(1.4)	4	(0.9)	12	(1.2)
Other	25	(4.3)	12	(2.7)	37	(3.6)
Unknown	8	(1.4)	9	(2.0)	17	(1.6)
Anatomic site						
Head	271	(46.6)	228	(50.4)	499	(48.3)
Trunk	71	(12.2)	46	(10.2)	117	(11.3)
Upper limb	120	(20.6)	79	(17.5)	199	(19.3)
Lower limb	84	(14.4)	81	(17.9)	165	(16.0)
Other‡	36	(6.2)	18	(4.0)	54	(5.2)
Stage at diagnosis						
Localized	282	(48.5)	225	(49.8)	507	(49.0)
Regional	160	(27.5)	121	(26.8)	281	(27.2)
Distant	46	(7.9)	35	(7.7)	81	(7.8)
Unstaged	94	(16.1)	71	(15.7)	165	(16.0)
Anatomic site by age at diagnosis						
<65 y						
Head	47	(29.8)	41	(46.1)	88	(35.6)
Trunk	34	(21.5)	14	(15.7)	48	(19.4)
Upper limb	29	(18.4)	18	(20.2)	47	(19.0)
Lower limb	34	(21.5)	11	(12.4)	45	(18.2)
Other‡	14	(8.9)	5	(5.6)	19	(7.7)
65-74 y						
Head	85	(50.0)	52	(46.9)	137	(48.8)
Trunk	14	(8.2)	7	(6.3)	21	(7.5)
Upper limb	43	(25.3)	24	(21.6)	67	(23.8)
Lower limb	22	(12.9)	22	(19.8)	44	(15.7)
Other‡	6	(3.5)	6	(5.4)	12	(4.3)
75+ y						
Head	139	(54.7)	135	(53.6)	274	(54.2)
Trunk	23	(9.1)	25	(9.9)	48	(9.5)
Upper limb	48	(18.9)	37	(14.7)	85	(16.8)
Lower limb	28	(11.0)	48	(19.1)	76	(15.0)
Other‡	16	(6.3)	7	(2.8)	23	(4.6)
Anatomic site by stage at diagnosis						
Localized						
Head	140	(49.6)	120	(53.6)	260	(51.3)
Trunk	27	(9.6)	12	(5.3)	39	(7.7)
Upper limb	70	(24.8)	51	(22.7)	121	(23.9)
Lower limb	44	(15.6)	39	(17.3)	83	(16.4)
Other‡	1	(0.4)	3	(1.3)	4	(0.8)

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*P < .0001.
†Percentages may not sum to 100 because of rounding.
‡Includes tumors overlapping with 2 or more anatomic sites.

Table I. Cont'd

	Males N = 582 (56.3%)		Females N = 452 (43.7%)		Total N = 1034	
	No.	(%)††	No.	(%)†	No.	(%)†
Anatomic site by stage at diagnosis (cont'd)						
Regional						
Head	66	(41.3)	63	(52.1)	129	(45.9)
Trunk	24	(15.0)	12	(9.9)	36	(12.8)
Upper limb	37	(23.1)	15	(12.4)	52	(18.5)
Lower limb	32	(20.0)	31	(25.6)	63	(22.4)
Other‡	1	(0.6)	0	(0.0)	1	(0.4)
Distant						
Head	21	(45.7)	15	(42.9)	36	(44.4)
Trunk	8	(17.4)	13	(37.1)	21	(25.9)
Upper limb	5	(10.9)	1	(2.9)	6	(7.4)
Lower limb	2	(4.4)	2	(5.7)	4	(4.9)
Other‡	10	(21.7)	4	(11.4)	14	(17.3)
Unstaged						
Head	44	(46.8)	30	(42.3)	74	(44.9)
Trunk	12	(12.8)	9	(12.7)	21	(12.7)
Upper limb	8	(8.5)	12	(16.9)	20	(12.1)
Lower limb	6	(6.4)	9	(12.7)	15	(9.1)
Other‡	24	(25.5)	11	(15.5)	35	(21.2)

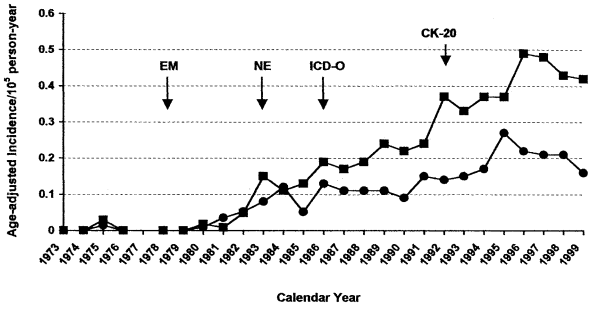

Fig 1. Primary Merkel cell carcinoma: Age-adjusted incidence per 100,000 person-years according to sex and calendar year at diagnosis (1973-1999, SEER Program studying 9 geographic areas). *Arrows* indicate introduction of: electron microscopy (*EM*)[16]; neuron-specific enolase (*NE*)[27-29]; *International Classification of Diseases for Oncology*, first update (*ICD-O*)[25]; and cytokeratin (*CK*)-20.[31] *Circles*, Females; *squares*, males.

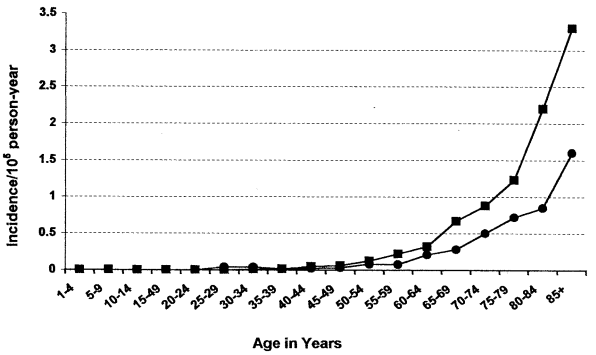

Fig 2. Primary Merkel cell carcinoma: Age-specific incidence per 100,000 person-years according to sex (1973-1999, SEER Program studying 9 geographic areas). *Circles*, Females; *squares*, males.

tion was present between the logarithms of the age-adjusted incidence of primary MCC and the UVB radiation indexes of the SEER geographic areas (SEER-9, 1986-1999) for cases of the head ($r = 0.84$, $P = .005$) (Fig 3) and for all cases ($r = 0.72$, $P = .03$), but not for all cases except the head ($r = -0.31$, $P = 0.4$) (data not shown).

For all cases, the 5-year observed survival rate was 45%; however, the 5-year relative survival rate was 62%. Curves for observed and relative survival, for relative survival according to stage and to anatomic site at diagnosis are shown in Fig 4. HRs and 95% CIs for age, stage, and anatomic site at diagnosis are shown in Table III. Females had a better probability of survival than males (HR = 0.83, 95% CI = 0.77-0.99), and this finding strengthened after controlling for age, stage at diagnosis, and anatomic site (HR = 0.71, 95% CI = 0.59-0.87).

DISCUSSION

The increase of the incidence rates of primary MCC over time seems to reflect the improvement in case finding and in histopathologic diagnosis, which has seen the relatively rapid introduction and diffusion of new diagnostic instruments, techniques, and biomarkers. The very few cases reported during the first 10 years may be indicative of difficulties in

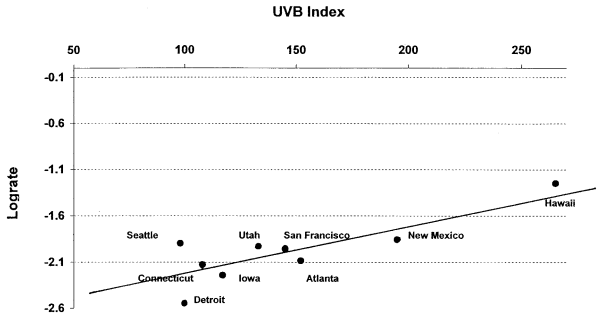

Fig 3. Primary Merkel cell carcinoma of head in whites: Linear correlation of age-adjusted incidence with UVB radiation indexes (1986-1999 SEER Program studying 9 geographic areas), $r = 0.84$, $P = .005$. *Lograte*, Natural logarithm of age-adjusted incidence rates per 100,000 person-years. UVB indexes from Scotto et al.[34,42]

Table II. Incidence per 100,000 person-years of primary Merkel cell carcinoma in the United States by sex, race, and age (1986-1999)*

Incidence	Men	Women	Total
All†	0.34	0.17	0.24
Race†			
White	0.38	0.19	0.26
Black	0.032	0.015	0.023
Other	0.14	0.095	0.12
Age groups (y)			
<65	0.08	0.05	0.06
≥65	2.13	1.00	1.42
65-74	1.24	0.60	0.89
≥75	3.10	1.44	2.00

*Surveillance, Epidemiology, and End Results (SEER) Program.
†Age-adjusted to the year 2000 standard population for the United States.

diagnosis and a low familiarity with this cancer by physicians. Other biomarkers, which could further facilitate MCC diagnosis, have been recently described.[45] It is possible that several more years of follow up will be needed to ascertain the steady incidence rate of primary MCC in the US population and to evaluate if better diagnosis and recognition of the disease may hide the presence of a true increase in the incidence rate of primary MCC over time, as has been reported for other nonmelanoma skin cancers.[46] The plateau or slight decline in incidence rates observed since 1996 could be due to either improved detection in 1990 to 1995, resulting in a greater increase in incidence for these years (period effect), or to late reporting.[47] Data would need to be analyzed again in a few years to ascertain which of these 2 factors may be responsible for the observed incidence trend.

Primary MCC remains a rare disease with an overall estimated age-adjusted incidence of 0.24 per 100,000 person-years. Our finding of a higher incidence in males than in females confirms previous reports for the SEER areas.[34] In agreement with published literature,[2-10] we found that primary MCC is essentially a disease of older whites. The incidence rate of primary MCC increased, overall, 24 times in people 65 years or older compared with younger people. The greatest increase was observed in people 65 to 74 years old, where the incidence rate was 15 times higher than in people younger than 65 years.

We found that the head was the most frequently involved anatomic site, as reported by most authors,[2,3,9,48-50] in each age group in both sexes, followed by upper limb, lower limb, and trunk. However, although in females the proportion of cases at the head remained approximately the same up to age 75 years and increased modestly in older females, in males the proportional involvement of the head increased almost 5 times from individuals less than 65 years of age to older individuals. The head, especially the face, is the anatomic area less protected from environmental elements. Our data suggest that cumulative damage secondary to chronic or repetitive injuries, either by exposure to sun or to other elements, may play a role in the etiology of primary MCC of the head. The differences in the 2 sexes could reflect an increased susceptibility to environmental exposure of the female skin[51] in younger years, whereas differences in lifestyle and in environmental exposure (eg, less use of creams with UV protection factors in males and/or major exposure to sun and environment) could account for the greater increase of MCC at the head in males in later years. Another intriguing finding was the greater proportion of cases at the trunk and at the limbs observed in males less than 65 years old compared with older males. The same trend was observed, to a lesser degree, in females, but conventional statistical significance was reached for males only. We do not have a ready explanation for this finding.

Overall, less than 50% of all cases were reported at stage I. A higher proportion (76%) of cases with localized disease at diagnosis has been reported by Allen et al[13] in one of the largest series studied (n = 102). This difference appears related to the different anatomic site most frequently affected at diagnosis in the population under study. In the series studied by Allen et al,[13] the extremities were the most frequently affected sites. In the present population-based study, the most frequently affected anatomic site was the head. We found that localization at the limbs was associated with less advanced stages at diagnosis compared with other anatomic sites.

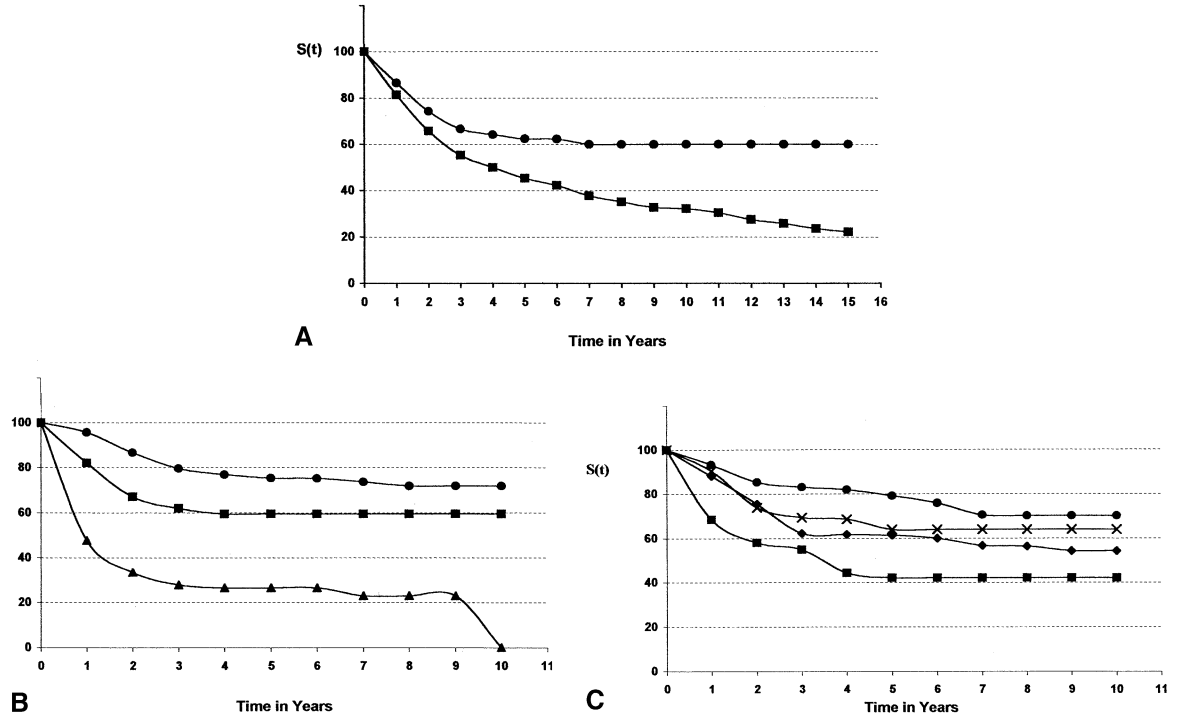

Fig 4. Primary Merkel cell carcinoma (1973-1999): observed (*square*) and relative (*circle*) survival (**A**); relative survival by stage (*circle*, localized; *square*, regional; or *triangle*, distant metastasis) (**B**); and anatomic site at diagnosis (*circle*, upper limb; *x*, lower limb; *diamond*, head; or *square*, trunk) (**C**). SEER Program, 9 geographic areas.

Published data on survival are limited and provide inconsistent information.[3] In our study, the relative probability of survival decreased sharply when MCC had progressed to regional and metastatic disease. Overall, 2 years after diagnosis, only 32% of patients with a stage III diagnosis survived compared with 86% of patients with a stage I diagnosis. The probability of survival decreased further to 25%, compared with 75%, 5 years after diagnosis. These data, together with the finding that less than 50% of cases were reported as localized disease, may indicate that the described unfavorable prognosis of MCC could be mostly due to late diagnosis. In both sexes, advanced age at diagnosis decreased survival independently from anatomic site and stage. In the eldest, possibly because of the frailty that accompanies this age group, even a localized disease seems to have a poor prognosis. The better survival observed in females, in agreement with some previous reports[2,6,9] but not with others,[2,13] could be related to biologic differences between the two sexes[51]; however, eventual variations in specific modalities of treatment for MCC were not studied and it is possible that they could affect survival differently in males and females. Survival was also associated with anatomic localization. All anatomic sites had a worse survival probability than the upper limb in both sexes; however, conventional statistical significance was reached only for localization at the head in males and at the trunk in females. The prognostic differences between men and women in relation to anatomic site could indicate variability in when, and for what, medical attention in sought. Even if we controlled for stage at diagnosis, tumor size and number of regional lymph nodes involved were not modeled. Females could seek medical care for a nodule at the face earlier than males, although it is also possible that the trunk in females is examined less frequently than in males either in the social or in the medical settings.

As with other nonmelanoma skin cancers that affect sun-exposed areas of the skin and that are prevalent in whites and fair-skinned people,[42,46] long-term exposure to solar UV radiation is considered an important risk factor for MCC.[2-10,34] Our data support the hypothesis of UVB radiation exposure as a risk factor for primary MCC of the head in whites.[34] It is less clear what role the cumulative exposure to sun, and to other environmental elements, could have in the etiology of primary MCC involving the extremities and the trunk, considering that there is no apparent relation between primary MCC of these sites and UVB radiation exposure, that these anatomic sites are less exposed to the environ-

Table III. Hazard ratios and 95% confidence intervals for primary Merkel cell carcinoma by age, stage, and anatomic site at time of diagnosis (1973-1999)*

	Males		Females	
	HR	**95% CI**	**HR**	**95% CI**
Age (y)†				
<65 (reference category)	1.0	—	1.0	—
65-74	1.5	1.1-2.1	1.4	0.8-2.3
75+	2.3	1.7-3.1	3.3	2.2-5.1
Stage at diagnosis‡				
Localized (reference category)	1.0	—	1.0	—
Regional	1.5	1.1-2.0	1.5	1.1-2.2
Distant	3.5	2.3-5.2	4.0	2.5-6.4
Unstaged	1.9	1.3-2.6	2.1	1.4-3.0
Anatomic site§				
Upper limb (reference category)	1.0	—	1.0	—
Head	1.7	1.2-2.3	1.2	0.8-1.8
Trunk	1.3	0.9-2.1	2.8	1.7-4.6
Lower limb	1.4	0.9-2.2	1.2	0.7-1.9
Other	1.1	0.6-1.9	1.0	0.5-2.3

CI, Confidence interval; *HR*, hazard ratio.
*SEER Program.
†Controlling for stage and anatomic site.
‡Controlling for age and anatomic site.
§Controlling for age and stage at diagnosis.

ment, and that the affected individuals are younger. Moreover, for primary MCC involving mucosal anatomic sites, it seems unlikely that exposure to sun and/or other elements could play a causal role. The small numbers of primary MCC identified at mucosal anatomic sites involved mostly those (nasal, oral, pharyngeal, and laryngeal mucosae) that are predisposed to lesions associated with smoking, alcohol intake, and trauma.[52] Considered as a whole, our data suggest that primary MCC is, probably, multifactorial in origin. It is possible that any damaged skin or mucosa, even if the damage precedes MCC by many years, and for any cause, be it long-term sun exposure,[34] phototherapy,[53] UVA radiation,[54] UVB radiation,[34,55] infrared radiation,[10] direct radiation of the skin,[56,57] long-term arsenic exposure,[58-60] congenital diseases,[2,50,61] other neoplastic lesion of the skin preceding MCC,[10,49,62,63] or an old burn scar[10,64] constitutes an area of increased susceptibility to MCC. People living in geographic areas with a high UVB solar index have a higher probability of injury to sun-exposed skin, especially of the face and of the head. Given the median age of cases with primary MCC, it is likely that several (minor) injuries of different kinds may affect the same skin area over time with a cumulative effect that could increase the frequency of genetic somatic mutations, possibly involving a tumor suppressor gene.[55,65-68]

MCC has been reported in association with immunosuppression secondary to either endogenous or exogenous causes.[2,6,10,69,70] The physiologic changes associated with aging include a decrease of cell-mediated and humoral immunity.[7] However, MCC is a very rare disease in contradistinction with what could be expected in a population, the elderly, with high prevalence of possible risk factors such as skin injury, long-term sun exposure, and a partially impaired immune system. The reasons for this apparent contradistinction are not self-evident. It could be that specific, still unknown events could cause (relative) immune suppression, greater than expected by age alone, in a small proportion of the elderly. Reports[10,71] of an increased number of second neoplasms either before, concomitant, or after MCC diagnosis seem to support this hypothesis. It would be of epidemiologic interest and of clinical use to study the comorbidity conditions of people affected by primary MCC to ascertain if their medical history is relevant for factors (eg, a disease, certain medical therapies) that could cause a depression of their immune system greater than expected by age alone.

MCC is essentially a disease of older whites with possible age- and sex-related differences in presentation. These differences are small and difficult to study because of the tumor's rarity, but they could explain many of the (apparent) inconsistencies in published reports concerning most frequently affected anatomic site, stage at diagnosis, and survival. The long follow-up time and the large number of

cases identified in this study allowed the evaluation of primary MCC incidence trends since its first description for males and females, of the distribution of cases in different age groups, of the association of anatomic site with stage at diagnosis, and of predictors of survival in the 2 sexes. Our data indicate that female sex, tumor presentation at the limbs, localized disease, and younger age at diagnosis are positive predictors of survival, whereas localization at the head in males and at the trunk in females are negative predictors of survival.

Our data indicate that most cases of primary MCC are diagnosed when the disease has already spread to regional lymph nodes (stage II) or distant sites (stage III) and that, for these patients, the probability of survival is already greatly reduced when the diagnosis is made. A late diagnosis may be a result of different causes that can be independent from each other or contributing to one another (eg, patients may delay seeking medical attention because the initial lesion is asymptomatic; this same aspecific, benign-appearing, insidious lesion could be initially considered as not worrisome by health professionals; a diagnostic biopsy could be postponed). A high degree of clinical awareness by physicians, when an asymptomatic, noncharacteristic cutaneous nodule is observed in older whites, the subgroup of the population at higher risk, with recognition of the aggressive nature of this tumor, could bring to earlier diagnosis and prompt treatment[7] and could greatly improve the probability of survival.

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