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ARTICLE

Merkel Cell Carcinoma: Incidence, Mortality, and Risk of Other Cancers

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Background Merkel cell carcinoma (MCC) is a rare skin cancer that was recently found to be associated with a polyomavirus and with immunosuppression, provoking new interest in its epidemiology. We conducted a nationwide study in Denmark to describe MCC incidence and mortality and the association between MCC and other cancers.

Methods We used data from Danish national health and population registers on MCC diagnoses, deaths, and population counts during the study period (1978–2006) to calculate MCC incidence rates, cumulative risks of MCC at age 100 years, and MCC mortality rates by tumor stage. We used Poisson regression to estimate the excess mortality rate ratio attributable to MCC and examined associations between MCC and other cancers diagnosed before and after the MCC diagnosis using standardized incidence rate ratios (SIRs). All statistical tests were two-sided.

Results Between January 1, 1978, and December 31, 2006, 185 persons were diagnosed with MCC in Denmark. MCC incidence between 1995 and 2006 was 2.2 cases per million person-years. In the first year after MCC diagnosis, 22% of persons with localized disease died compared with 54% of patients with nonlocalized disease; by 5 years after diagnosis, the proportions of MCC patients who had died increased to 55% and 84%, respectively. MCC incidence was statistically significantly increased more than 1 year after a diagnosis of squamous cell carcinoma of the skin (SIR = 14.6, 95% confidence interval [CI] = 8.4 to 25.6), basal cell carcinoma (SIR = 4.3, 95% CI = 2.7 to 6.6), malignant melanoma (SIR = 3.3, 95% CI = 1.1 to 10.3), chronic lymphocytic leukemia (SIR = 12.0, 95% CI = 3.8 to 37.8), Hodgkin lymphoma (SIR = 17.6, 95% CI = 2.5 to 126), and non-Hodgkin lymphoma (SIR = 5.6, 95% CI = 1.4 to 22.4). Squamous cell carcinoma (SIR = 12.1, 95% CI = 5.1 to 29.1) and chronic lymphocytic leukemia (SIR = 14.7, 95% CI = 3.7 to 58.8) occurred in statistically significant excess more than 1 year after MCC diagnosis.

Conclusions These results support the existence of shared risk factors for MCC and other cancers. Heightened awareness of the association between MCC and other cancers, particularly squamous cell carcinoma and chronic lymphocytic leukemia, may facilitate earlier clinical detection and treatment of MCC, thereby improving patient survival.

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Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine skin cancer that occurs more frequently in immunosuppressed individuals, such as those infected with HIV and/or diagnosed with AIDS (1,2). In 2008, a previously unknown polyomavirus designated Merkel cell polyomavirus (MCV) was found in MCC tumors; MCV DNA sequences were detected in eight (80%) of the 10 MCC tumors compared with only four (16%) of the 25 control skin tissue samples (3).

Many individuals who are diagnosed with MCC have a history of other sun exposure–associated skin cancers (4,5), and MCC may also share etiologic factors with other malignancies. For example, increased joint risks of MCC and multiple myeloma (4), chronic lymphocytic leukemia (4,6), non-Hodgkin lymphoma (4,6), and malignant melanoma (4,5) have been reported but have not been explained.

These findings have provoked a new interest in the epidemiology of MCC and in investigating the co-occurrence of MCC and other cancers. In this study, we used Danish national health and population registers to examine MCC incidence, MCC mortality by stage at diagnosis, and the association between MCC and the risk of other cancers, particularly the risks of basal cell carcinoma and squamous cell carcinoma of the skin before and after MCC diagnosis.

Methods

This study was approved by the Danish Data Protection Agency.

Identification of Persons with Cancer

Persons with incident cancer diagnosed from January 1, 1978, through December 31, 2006, were identified using the Danish Cancer Register. The Danish Cancer Register is considered close to complete (95%–98%) for incident cases of cancer diagnosed in

CONTEXT AND CAVEATS

Prior knowledge

Merkel cell carcinoma (MCC) is a rare aggressive skin cancer that was recently linked to a previously unknown polyomavirus. MCC occurs more frequently in immunosuppressed individuals, and many individuals who are diagnosed with MCC have a history of other cancers, including sun exposure–associated skin cancers, suggesting that MCC may also share etiologic factors with other malignancies.

Study design

Data from Danish national health and population registers were used to describe MCC incidence, MCC mortality by stage at diagnosis, and associations between MCC risk and the risks of other cancers.

Contribution

Overall MCC incidence was higher among women than among men and among older individuals. MCC patients had a higher mortality than was expected due to advanced age alone. MCC mortality did not differ by location of the primary tumor. There was an increased risk of being diagnosed with MCC more than 1 year after a diagnosis of basal cell carcinoma, squamous cell carcinoma of the skin, cutaneous malignant melanoma, chronic lymphocytic leukemia, Hodgkin lymphoma, or non-Hodgkin lymphoma, and there were increased risks of squamous cell carcinoma of the skin, chronic lymphocytic leukemia, and other cancers diagnosed more than 1 year after MCC diagnosis.

Implications

There may be shared risk factors for MCC and other cancers. Heightened awareness of the association between MCC and other cancers may facilitate earlier clinical detection and treatment of MCC.

Limitations

Misclassification of cancers because of incomplete or inaccurate registration of diagnoses is a possibility in any register-based study. Surveillance bias is a possible (but unlikely) explanation for the observed associations between MCC and squamous cell carcinoma.

From the Editors

Denmark since 1943 (7) because physicians are required by law to report each cancer diagnosis, along with the primary tumor site and stage, to the register at the time of diagnosis. In addition, pathology and forensic medicine departments are required to report cancer information to the register. All cancer-specific autopsy information is reported to the register, regardless of whether the deceased was known to have cancer or the cancer was first noted at autopsy. Finally, cancer diagnoses registered in the Danish Hospital Discharge Register or the National Causes of Death Register, but not reported to the Danish Cancer Register (for whatever reason), are added to the Danish Cancer Register annually.

Cancers in the Danish Cancer Register are categorized according to *International Classification of Diseases*, *Seventh Revision* (*ICD-7*), codes, with conversion to the equivalent *ICD*, *Tenth Revision* (*ICD-10*), codes (8). Malignant melanoma is designated by the *ICD-10* code C43, whereas nonmelanoma skin cancers receive the *ICD-10* code C44 and are distinguished from one another using additional histology codes. MCC was first described in 1972 (9,10) and since 1978 has been designated by the *ICD-10* code C44 combined with the histology code 82473. We grouped other nonmelanoma skin cancers into squamous cell carcinoma (C44, histology codes 80513–80523, 80703–80763, 80943, or 85603) and basal cell carcinoma (C44, histology codes 80903–80933). Tumor staging in the Danish Cancer Register follows the International Union Against Cancer TNM Classification of Malignant Tumors (11).

Identification of Person with HIV/AIDS

Persons with HIV/AIDS were identified using the Danish Hospital Discharge Register (*ICD*, *Eighth Revision* [*ICD-8*], Danish version (12) code 079.83 and *ICD-10* codes B20–B24). Data on all nonpsychiatric inpatient hospitalizations in Denmark have been reported to the Danish Hospital Discharge Register since 1977, and all outpatient visits have been reported since 1995.

Statistical Analyses

We estimated MCC incidence rates in the cohort of all persons residing in Denmark during the period January 1, 1978, to December, 31 2006, as identified by using the Civil Registration System (CRS). All residents of Denmark are registered in the CRS by means of a personal identification number, and information on their vital status, emigration, or disappearance is updated daily, which permits virtually complete follow-up of study subjects who live in Denmark and linkage with Danish population-based health registers. MCC incidence rates were estimated as number of MCC patients registered during the follow-up period divided by the number of years of follow-up. In the estimation of rates for the entire study period, each person was followed up from January 1, 1978, or the date of birth, whichever came later, to the date of MCC diagnosis, death, emigration, being recorded as a missing person in the CRS, or December 31, 2006, whichever occurred first. We also estimated 5-year incidence rates for the periods 1985–1989, 1990–1994, and 1995–1999, as well as incidence rates for the periods 1978–1984 and 2000–2006. Because there were too few cases in the periods 1978–1979 and 2005–2006 to allow for the estimation of stable rates for these periods alone, we combined these periods with the 5-year periods 1980–1984 and 2000–2004, respectively, when estimating period-specific incidence rates. Cumulative risk of MCC at age 100 years was estimated as 1 minus $\exp(-\Lambda)$, where Λ is the cumulative incidence rate determined as a weighted sum of age-specific incidence rates with weights equal to the number of years in the age categories. We chose to estimate cumulative risk up to age 100 years because of the relatively high incidence of MCC even at age 90 years or older, which allowed for a simple overall evaluation of sex differences not attributable to differences in average life expectancy.

MCC mortality was estimated in the cohort of MCC patients who were diagnosed between January 1, 1978, and December 31, 2006, with follow-up from the date of MCC diagnosis to the date of death, emigration, being recorded as a missing person in the CRS, or December 31, 2008, whichever occurred first. The percentages of patients with known tumor stage who were alive after diagnosis, by tumor stage, were estimated by Kaplan–Meier analyses and compared with the percentages expected to be alive in

the absence of MCC based on national age-, period-, and sex-specific mortality rates estimated using information from the CRS. The excess mortality rate ratio attributable to MCC was evaluated by using a Poisson regression model, with the observed number of deaths as the outcome, the logarithm of the number of person-years at risk as the offset, and adjustment for stage at diagnosis (localized, nonlocalized, unspecified, or unstaged), sex, and number of years since diagnosis (<1, 1, 2–4, and ≥5 years). For each unique combination of covariates, *i*, the mean parameter was modeled as $\exp(X_i'\beta) \times \mathrm{PY}_i + E_i$, where X_i is the vector of covariates, β is the vector of regression parameters, PY_i is the number of person-years, and E_i is the expected number of cancers. The model can be viewed as a log-linear model of the observed death rate in MCC patients minus the expected death rate, that is, a model of the excess mortality rate attributable to MCC. Consequently, we interpreted the estimated rate ratios as ratios of excess mortality rates attributable to MCC and designated them excess mortality rate ratios. Excess mortality rates were estimated by using a regression model that was similar to the one described above except that it did not include an intercept or other covariates.

We estimated the standardized incidence rate ratios (SIRs) of MCC after a diagnosis of cancer at selected sites with follow-up from the date of cancer diagnosis or January 1, 1978, whichever came last, to the date of MCC diagnosis, death, emigration, being recorded as a missing person in the CRS, or December 31, 2006, whichever occurred first. Standardized incidence rate ratios of selected cancers after a primary MCC diagnosed from January 1, 1978, to December 31, 2006, were estimated with follow-up from the date of the MCC diagnosis to the date of diagnosis of cancer at the selected site, death, emigration, being recorded as a missing person in the CRS, or December 31, 2006, whichever occurred first. Standardized incidence rate ratios were calculated as the observed number of cases divided by the expected number of cancers. The expected number of cancers was estimated by using national age-, period-, and sex-specific cancer rates from the Danish Cancer Register. We estimated 95% confidence intervals (CIs) by assuming a Poisson distribution for the observed cancers. All tests of differences were likelihood ratio tests. *P* values are two-sided, and *P* values less than .05 were considered statistically significant.

Results

Characteristics of MCC Patients

Between January 1, 1978, and December 31, 2006, 185 people were diagnosed with MCC in Denmark. In general, MCC patients were elderly: 90.8% were 65 years or older at the time of diagnosis, and 58.4% were older than 75 years (Table 1). The most frequent primary tumor site was the head (46%), followed by the lower limbs (13%), upper limbs (12%), and the trunk (9%). More than half of the patients were diagnosed with localized MCC (Table 1). Among patients with nonlocalized disease (ie, those with regional or distant metastases), the most common anatomical location of the primary MCC tumor was the head (Table 1). None of the MCC patients were diagnosed with HIV/AIDS either before or after the MCC diagnosis, as expected; in Denmark, only 250–300 persons (13) among a total population of approximately 5 519 441 (14) are diagnosed with HIV/AIDS annually.

Table 1. Distribution of Merkel cell carcinoma cases in Denmark, 1978–2006

Characteristic	Men (n = 74)	Women (n = 111)	Total (n = 185)
Age at diagnosis, y			
Median	76.5	80.0	78.0
Mean	75.6	78.1	77.1
Range	48–95	34–98	34–98
Age at diagnosis (y), No. (%)			
<40	0 (0)	2 (2)	2 (1)
40–49	1 (1)	2 (2)	3 (2)
50–59	4 (5)	3 (3)	7 (4)
60–69	13 (18)	11 (10)	24 (13)
70–79	32 (43)	35 (32)	67 (36)
80–89	18 (24)	42 (38)	60 (32)
≥90	6 (8)	16 (14)	22 (12)
Year of diagnosis, No. (%)			
1978–1984	0 (0)	2 (2)	2 (1)
1985–1989	1 (1)	9 (8)	10 (5)
1990–1994	13 (18)	25 (23)	38 (21)
1995–1999	27 (37)	30 (27)	57 (31)
2000–2004	24 (32)	29 (26)	53 (29)
2005–2006	9 (12)	16 (14)	25 (14)
Anatomical location at diagnosis, No. (%)			
Head	33 (45)	52 (47)	85 (46)
Trunk	9 (12)	7 (6)	16 (9)
Upper limb	8 (11)	14 (13)	22 (12)
Lower limb	6 (8)	18 (16)	24 (13)
Unspecified	18 (24)	20 (18)	38 (21)
Stage* at diagnosis, No. (%)			
Localized	36 (49)	65 (59)	101 (55)
Regional metastases	10 (14)	14 (13)	24 (13)
Distant metastases	10 (14)	3 (3)	13 (7)
Unstaged	18 (24)	29 (26)	47 (25)
Anatomical location by stage at diagnosis, No. (%)			
Localized			
Head	20 (27)	35 (32)	55 (30)
Trunk	5 (7)	2 (2)	7 (4)
Upper limb	5 (7)	10 (9)	15 (8)
Lower limb	3 (4)	13 (12)	16 (9)
Nonlocalized			
Head	8 (11)	8 (7)	16 (9)
Trunk	3 (4)	2 (2)	5 (3)
Upper limb	1 (2)	3 (3)	4 (2)
Lower limb	2 (3)	0 (0)	2 (1)
Unstaged or unspecified location	27 (37)	38 (34)	65 (35)

* Tumors were staged using the International Union Against Cancer TNM Classification of Malignant Tumors (11).

MCC Incidence

We examined MCC incidence rates by calendar period (Figure 1). From January 1, 1978, to December 31, 1984, only a few (<20) incident cases of MCC were reported to the Danish Cancer Register. MCC incidence increased progressively between 1985 and 1994. Between 1995 and 2006, MCC incidence was stable at 2.2 cases per million person-years; MCC incidence during this period among men and women was 2.0 and 2.5 cases per million person-years, respectively. The higher overall incidence in women was primarily because of their longer life spans; as illustrated in Figure 2, the age-specific incidence of MCC was very similar for men and women. Furthermore, estimates of cumulative risk of MCC at age 100 years were very similar: 838 cases per million

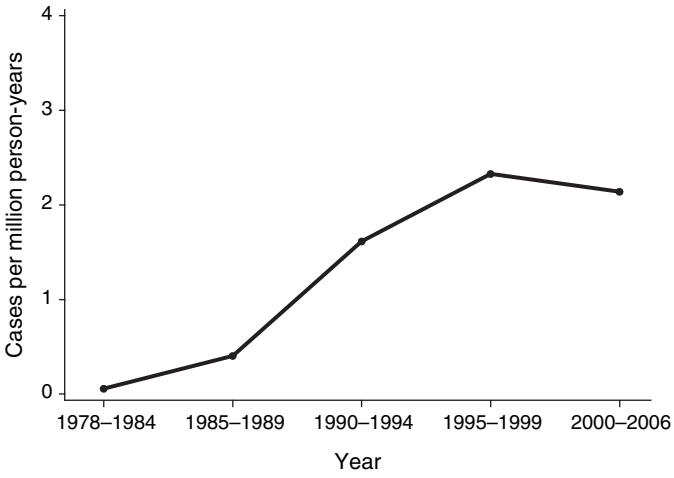

Figure 1. Incidence of Merkel cell carcinoma in Denmark, 1978–2006, by calendar period.

person-years in men vs 849 cases per million person-years in women. MCC incidence was very low among those younger than 60 years (on average, 0.19 cases per million person-years). MCC incidence increased to 11.3, 19.5, and 50.3 cases per million persons-years among individuals who were 70–79 years old, those who were 80–89 years old, and those who were 90 years or older, respectively.

MCC Mortality

During 682 person-years of follow-up, 162 of the 185 MCC patients died. The mortality rate among men was twice that among women (Table 2). We examined the proportion of MCC patients who were alive by time since and stage at diagnosis (Figure 3). One year after MCC diagnosis, 22% of patients with localized MCC had died, whereas 54% of patients with nonlocalized MCC had died. Five years after MCC diagnosis, 55% and 84% of the patients with localized and nonlocalized MCC, respectively, had died. However, the observed high mortality was partly because of the advanced age of the majority of MCC patients; even without an MCC diagnosis, almost 8% of the patient cohort were expected to die (of old age) within 1 year of the start of follow-up, and 33% were expected to die within 5 years (Figure 3). We therefore estimated the excess mortality rate attributable to MCC, which is a less age-dependent mortality measure. The excess mortality rate attributable to MCC within 1 year of MCC diagnosis was 8.4 deaths per 100 person-years (95% CI = 5.5 to 12.7 deaths per 100 person-years) for localized MCC and 32 deaths per 100 person-years (95% CI = 21.3 to 48.1 deaths per 100 person-years) for nonlocalized MCC (Table 2).

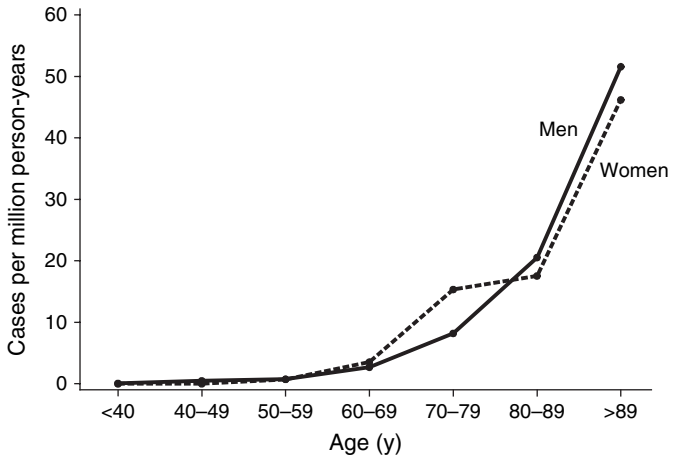

Figure 2. Incidence of Merkel cell carcinoma in Denmark, 1978–2006, by age and sex.

MCC and Other Cancers

The 185 MCC patients had been diagnosed with 121 other cancers more than 1 year before their MCC diagnosis. The MCC incidence rate more than 1 year after the diagnosis of another cancer was 2.6 times higher (95% CI = 1.8 to 3.6 times higher) than expected based on the MCC incidence in the general Danish population (Table 3). This excess risk was seen both in women (SIR = 1.8, 95% CI = 1.2 to 2.9) and in men (SIR = 4.0, 95% CI = 2.5 to 6.6). There was a statistically significant elevated risk of being diagnosed with MCC more than 1 year after a diagnosis of any skin cancer (SIR = 2.6, 95% CI = 1.8 to 3.6), basal cell carcinoma (SIR = 4.3, 95% CI = 2.7 to 6.6), squamous cell carcinoma of the skin (SIR = 14.6, 95% CI = 8.4 to 25.6), cutaneous malignant melanoma (SIR = 3.3, 95% CI = 1.1 to 10.3), chronic lymphocytic leukemia (SIR = 12.0, 95% CI = 3.8 to 37.8), Hodgkin lymphoma (SIR = 17.6, 95% CI = 2.5 to 126), or non-Hodgkin lymphoma (SIR = 5.6, 95% CI = 1.4 to 22.4) (Table 3).

Conversely, during 682 years of follow-up, the 185 MCC patients were diagnosed with 43 other cancers more than 1 year after their MCC diagnosis. Overall cancer incidence in MCC patients more than 1 year after MCC diagnosis was more than twice that expected from the overall cancer incidence in the general Danish population (observed vs expected number of new cancers: 16 vs 6.9; SIR = 2.3, 95% CI = 1.4 to 3.8) (Table 3). This excess risk of other cancers was seen both in women (SIR = 2.3, 95% CI = 1.3 to 4.2) and in men (SIR = 2.3, 95% CI = 1.0 to 5.6). Squamous cell carcinoma of the skin (SIR = 12.1, 95% CI = 5.1 to 29.1) and chronic lymphocytic leukemia (SIR = 14.7, 95% CI = 3.7 to 58.8) occurred in statistically significant excess more than 1 year after MCC diagnosis compared with the general population of Denmark (Table 3).

Discussion

This study provides national incidence and mortality figures for MCC in Denmark and documents strong associations between MCC and other cancers, particularly squamous cell carcinoma of the skin and chronic lymphocytic leukemia. These findings suggest the existence of shared risk factors for MCC and other cancers.

We found that the incidence of primary MCC increased during the study period. This increase probably reflects increasing awareness and registration of MCC between 1978 and 1995, along with improvements in diagnostic methods. Since 1995, MCC incidence has been stable, probably because of more consistent recognition of this rare cancer by clinicians. The overall incidence of 2.2 cases of MCC per million person-years that we observed during the period 1995–2006 is similar to the incidence of MCC that has been

Table 2. Excess mortality rate ratio for Merkel cell carcinoma in Denmark, 1978 to 2006, by characteristics at diagnosis*

Characteristic	No. of deaths	Excess mortality rate per 100 person-years (95% CI)	Adjusted† excess mortality rate ratio (95% CI)	$P_{homogeneity}$‡
Sex				.001
Women	94	9.5 (6.5 to 13.9)	1.00 (referent)	
Men	68	26.9 (19.6 to 36.8)	2.28 (1.38 to 3.76)	
Age at diagnosis, y				.65
<75	35	13.4 (9.1 to 19.8)	1.00 (referent)	
≥75	127	15.0 (11.0 to 20.4)	1.12 (0.69 to 1.83)	
Year of diagnosis				.21
1978–1994	22	8.4 (3.8 to 18.5)	0.47 (0.19 to 1.20)	
1995–1999	54	16.3 (10.9 to 24.4)	0.81 (0.47 to 1.41)	
2000–2006	86	15.4 (11.1 to 21.5)	1.00 (referent)	
No. of years since diagnosis				<.001
0	62	30.7 (22.3 to 42.3)	2.58 (1.21 to 5.49)	
1	28	18.4 (11.0 to 30.9)	1.65 (0.69 to 3.96)	
2–4	32	5.3 (2.1 to 13.1)	0.65 (0.23 to 1.83)	
≥5	40	8.4 (4.4 to 16.1)	1.00 (referent)	
Anatomical location at diagnosis				.90
Head	77	12.9 (8.7 to 19.0)	1.06 (0.46 to 2.42)	
Trunk	12	13.7 (6.7 to 28.3)	0.98 (0.35 to 2.75)	
Upper limb	19	17.0 (9.1 to 31.8)	1.49 (0.57 to 3.89)	
Lower limb	21	10.1 (4.8 to 21.3)	1.00 (referent)	
Unspecified	33	22.5 (13.7 to 36.9)	1.19 (0.49 to 2.88)	
Stage at diagnosis				<.001
Localized	88	8.4 (5.5 to 12.7)	1.00 (referent)	
Nonlocalized	36	32.0 (21.3 to 48.1)	3.22 (1.83 to 5.66)	
Unspecified or unstaged	38	26.8 (17.5 to 41.0)	2.14 (1.16 to 3.94)	
History of other cancers				.77
Skin cancer	29	19.9 (11.6 to 34.0)	1.12 (0.61 to 2.05)	
Non-skin cancer	11	11.4 (4.8 to 27.3)	0.78 (0.32 to 1.90)	
No history	122	13.7 (10.3 to 18.3)	1.00 (referent)	

* CI = confidence interval.

† Adjusted for stage, sex, and number of years since diagnosis.

‡ *P* value for homogeneity of adjusted excess mortality rate ratios calculated for the categories of each characteristic. The *P* values are based on likelihood ratio tests and are two-sided.

reported in other European studies (10,15). Consistent with the published literature (10,16), we found that MCC is predominantly a disease of the elderly.

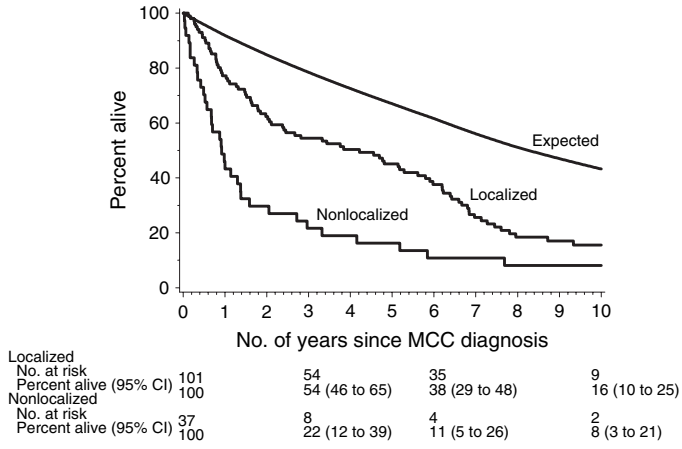

Figure 3. Kaplan–Meier analysis of the percentage of Merkel cell carcinoma (MCC) patients alive by number of years since diagnosis with localized or nonlocalized disease, compared with the percentage of patients expected to be alive had they not been diagnosed with MCC, based on national age-, period-, and sex-specific mortality rates. Unstaged MCC patients (n = 47) were not included in this analysis. CI = confidence interval.

We observed a higher overall MCC incidence among women than among men. This difference appeared to reflect the larger proportion of women than men who were in the oldest age groups, in which MCC incidence was highest. Other studies have reported a higher MCC incidence in men than in women (5,16,17). For example, an American study (16) found an MCC incidence among women (2.2 cases per million person-years) that was similar to the incidence we observed but reported a higher incidence among men (five cases per million person-years) than we observed. Persons with HIV/AIDS have previously been reported to have an approximately 11-fold higher incidence of MCC compared with the general population (1). The higher incidence of MCC among men in the American study may therefore be because of a greater number of HIV-positive and/or AIDS-affected men in the US Surveillance, Epidemiology, and End Results study population compared with the Danish population (16); indeed, we identified no cases of HIV/AIDS among the MCC patients in our study population. However, the American study also found a higher incidence of MCC among older men (16), suggesting that factors other than HIV infection may be involved in the excess risk of MCC in men.

Few data on the prognosis of MCC patients are available. The poorer prognosis associated with male sex that we observed is in agreement with the results of most (6,16,18–20), but not all (21),

Table 3. Risk of Merkel cell carcinoma (MCC) following specific cancer diagnoses and risk of specific cancers following an MCC diagnosis in Denmark, 1978–2006*

	Risk of MCC after other cancer diagnosis						Risk of cancer after MCC diagnosis					
	All subsequent MCC			MCC occurring >1 y after other cancer diagnosis			All subsequent cancers			Cancers occurring >1 y after MCC diagnosis		
Type of cancer	O	E	SIR (95% CI)	O	E	SIR (95% CI)	O	E	SIR (95% CI)	O	E	SIR (95% CI)
Any†	57	23.0	2.6 (1.9 to 3.6)	51	20.9	2.6 (1.8 to 3.6)	22	9.2	2.4 (1.6 to 3.6)	16	6.9	2.3 (1.4 to 3.8)
Skin cancer†	36	8.7	4.3 (3.0 to 6.2)	34	8.1	4.4 (3.0 to 6.5)	9	2.5	3.7 (1.9 to 7.1)	7	1.9	3.8 (1.8 to 7.9)
BCC	26	6.5	4.2 (2.8 to 6.4)	24	5.9	4.3 (2.7 to 6.6)	3	1.9	1.6 (0.5 to 4.9)	1	1.5	0.7 (0.1 to 4.9)
SCC	15	1.2	13.5 (7.9 to 23.3)	14	1.0	14.6 (8.4 to 25.6)	6	0.6	10.9 (4.9 to 24.4)	5	0.4	12.1 (5.1 to 29.1)
CMM	3	1.0	3.0 (1.0 to 9.5)	3	0.9	3.3 (1.1 to 10.3)	1	0.3	3.8 (0.5 to 26.7)	1	0.2	4.9 (0.7 to 35.0)
Other skin	1	0.2	4.9 (0.7 to 35.1)	2	0.8	3.2 (0.8 to 12.8)	0	0.1	—	0	0.1	—
Non-skin cancer†	28	18.2	1.6 (1.1 to 2.4)	22	16.4	1.4 (0.9 to 2.2)	20	9.0	2.2 (1.4 to 3.4)	14	6.7	2.1 (1.2 to 3.5)
Oral cavity	2	0.7	3.0 (0.8 to 12)	1	0.6	1.7 (0.2 to 11.8)	1	0.2	5.1 (0.7 to 35.7)	0	0.1	—
Digestive organs	5	4.3	1.2 (0.5 to 2.9)	4	3.7	1.1 (0.4 to 3.0)	5	3.2	1.6 (0.7 to 3.8)	3	2.4	1.3 (0.4 to 3.9)
Bone	0	0.0	—	0	0.0	—	0	0.0	—	0	0.0	—
Connective tissue	1	0.1	8.7 (1.2 to 62.4)	1	2.2	0.6 (0.1 to 4.0)	1	0.0	21.6 (3.0 to 154	0	0.0	—
Respiratory organs	1	0.9	1.2 (0.2 to 8.2)	0	0.6	—	5	1.4	3.6 (1.5 to 8.6)	3	1.0	2.9 (1.0 to 9.1)
Breast	3	4.6	0.7 (0.2 to 2.1)	1	4.2	0.2 (0.0 to 1.7)	1	1.4	0.7 (0.1 to 5.1)	1	1.1	0.9 (0.1 to 6.4)
Female genitourinary tract	4	3.4	1.2 (0.4 to 3.2)	4	3.2	1.2 (0.5 to 3.3)	0	0.7	—	0	0.5	—
Male genitourinary tract	2	1.8	1.1 (0.3 to 4.7)	2	1.5	1.4 (0.3 to 5.7)	1	1.1	0.9 (0.1 to 6.7)	1	0.8	1.3 (0.2 to 9.4)
Urinary tract	4	2.4	1.6 (0.6 to 4.4)	3	2.2	1.4 (0.4 to 4.3)	1	0.9	1.1 (0.2 to 8.0)	1	0.6	1.6 (0.2 to 11.0)
Brain, nervous system	1	0.6	1.7 (0.2 to 11.8)	1	0.6	1.8 (0.3 to 12.8)	1	0.2	4.3 (0.6 to 30.6)	1	0.2	5.8 (0.8 to 41.1)
Lymphatic malignancies	4	0.6	6.4 (2.4 to 17.2)	3	0.5	5.7 (1.8 to 17.7)	0	0.4	—	0	0.3	—
Hodgkin lymphoma	1	0.1	16.6 (2.3 to 119)	1	0.1	17.6 (2.5 to 126)	0	0.0	—	0	0.0	—
Non-Hodgkin lymphoma	3	0.4	7.3 (2.3 to 22.8)	2	0.4	5.6 (1.4 to 22.4)	0.3	0.0	—	0	0.2	—
Multiple myeloma	0	0.1	—	0	0.1	—	0	0.1	—	0	0.1	—
Mycosis fungoides	0	0.02	—	0	0.0	—	0	0.0	—	0	0.0	—
Hematologic malignancies	3	0.4	8.4 (2.7 to 26.2)	3	0.3	10.2 (3.3 to 31.9)	2	0.3	6.1 (1.5 to 24.3)	2	0.3	8.1 (2.0 to 32.5)
CLL	3	0.3	10.2 (3.2 to 31.9)	3	0.3	12.0 (3.8 to 37.8)	2	0.2	11.0 (2.7 to 43.8)	2	0.1	14.7 (3.7 to 58.8)
Myeloid leukemia	0	0.0	—	0	0.0	—	0	0.1	—	0	0.1	—
Monocytic leukemia	0	0.0	—	0	0.0	—	0	0.0	—	0	0.1	—
Other leukemia	0	0.0	—	0	0.0	—	0	0.0	—	0	0.0	—
Other cancer‡	1	0.3	3.2 (0.4 to 22.5)	0	0.3	—	5	0.6	8.3 (3.5 to 20.1)	3	0.5	6.6 (2.1 to 20.4)

* — = SIRs could not be calculated for these categories; BCC = basal cell carcinoma; CI = confidence interval; CLL = chronic lymphocytic leukemia; CMM = cutaneous malignant melanoma; E = expected; O = observed; SCC = squamous cell carcinoma; SIR = standard incidence rate ratio.

† The number of cases in this category is less than the sum of the cases in the subgroups because some individuals had several cancers.

‡ All other malignant neoplasms that do not fit into one of the named categories.

previous studies. We observed that MCC patients had a higher mortality than was expected due to advanced age alone. More than half of the MCC patients in this study had localized disease at the time of diagnosis, similar to findings reported by Agelli and Clegg (16). As might be expected, mortality was higher among MCC patients who had regional or metastatic disease at the time of diagnosis. The high excess mortality attributable to advanced (ie, nonlocalized) MCC, together with the finding that only approximately half of the MCC patients had localized disease at the time of diagnosis, suggests that earlier diagnosis might considerably improve the prognosis of MCC patients. Earlier diagnosis might not improve the prognosis for patients with immunosuppression-related MCC, however, because immunosuppression itself is often associated with increased mortality. Nevertheless, none of the MCC patients in our study were HIV positive, which decreased the likelihood that the observed excess mortality attributed to MCC was caused by immunosuppressive conditions alone.

We observed no differences in mortality by location of the primary tumor. Previous studies (9,10) have found that the anatomical location of the primary MCC tumor was associated with mortality: Tumors on the lower limbs in particular were found to be associated with increased mortality. Poulsen (9) explained these findings by speculating that poorer blood circulation in the lower limbs of elderly patients limits surgical resection and results in poor tolerance of high-dose radiation. By contrast, a recent analysis of 3870 MCC patients based on US Surveillance, Epidemiology, and End Results data found that the highest mortality was associated with MCC tumors on the trunk (22).

We found no differences in mortality by age at diagnosis once we had taken expected mortality into account by estimating excess mortality. Although Agelli and Clegg (16) found that patients who were older than 65 years at diagnosis had a higher observed mortality than younger patients, their analysis was not adjusted for the higher expected mortality due to advanced age itself.

It has been suggested that MCC patients with MCV-positive tumors might have better survival than those with MCV-negative tumors (23). The many competing causes of death in the elderly make MCC survival studies challenging, however, and a much larger dataset than ours would be needed to definitively address whether prognosis is related to tumor MCV status.

We found statistically significant increased risks of being diagnosed with MCC more than 1 year after a diagnosis of basal cell carcinoma, squamous cell carcinoma of the skin, cutaneous malignant melanoma, chronic lymphocytic leukemia, Hodgkin lymphoma, or non-Hodgkin lymphoma. Similarly, in a study based on Surveillance, Epidemiology, and End Results data, Howard et al. (4) reported an increased risk of MCC in patients who had previously been diagnosed with chronic lymphocytic leukemia, non-Hodgkin lymphoma, or cutaneous malignant melanoma compared with patients with no such earlier malignancies; they also found an increased risk of MCC in those previously diagnosed with multiple myeloma. Other small descriptive studies and case reports have suggested that the risk of MCC may increase after a diagnosis of multiple myeloma, non-Hodgkin lymphoma, or malignant melanoma (1,5,24).

We observed statistically significant increased risks of squamous cell carcinoma of the skin, chronic lymphocytic leukemia, and other cancers diagnosed more than 1 year after MCC diagnosis. We did not observe an excess of lymphoma subsequent to MCC, as has previously been reported (4,5,25).

The association of MCC with other cancers suggests that, at least in theory, MCV could play a role in malignancies other than MCC. Human exposure to MCV is common during childhood or young adulthood, and up to 80% of healthy adults are MCV seropositive by age 50 years (26,27). Evidence for the presence of MCV in tumors other than MCC is mixed: Becker et al. (28) failed to find evidence of MCV infection in patients with squamous cell carcinoma of the skin or basal cell carcinoma, whereas Kassem et al. (29) reported that immunosuppressed patients who had either of these cancers or Bowen disease were frequently infected with MCV. The results of Kassem et al. were not supported by a subsequent survey of tumors from organ transplant recipients (30). Direct immunostaining for viral protein also failed to demonstrate the presence of MCV in squamous cell carcinoma of the skin or basal cell carcinoma tumors, even among patients with concurrent MCC (31,32). In addition, although a variety of hematolymphoid cancers display low levels of MCV in polymerase chain reaction assays, MCV at levels consistent with viral presence in most of the tumor cells has not been observed in any single tumor type, including chronic lymphocytic leukemia (33). Although these studies do not rule out that MCV may contribute to some hematolymphoid tumors through an immunostimulatory mechanism or to a subset of hematolymphoid tumors that have not yet been examined, they raise the possibility that MCC shares nonviral risk factors with other tumors.

Our observation of increased risks of chronic lymphocytic leukemia both before and after an MCC diagnosis suggests the importance of immunologic factors in the etiology of MCC. Because these increased risks were observed more than 1 year before and after MCC diagnosis, they are unlikely to be due to surveillance bias, which is more likely for cases that are diagnosed within 1 year of MCC diagnosis as, for example, in the study by Howard et al. (4). However, our observation of substantially increased risk of chronic lymphocytic leukemia subsequent to MCC requires confirmation because it was based on small numbers and thus may represent a chance finding.

We observed strong associations between MCC and squamous cell carcinoma. Although patients with both conditions have been identified previously (20,24,34,35), a population-based assessment of the joint risk of MCC and squamous cell carcinoma has to our knowledge never been undertaken. Because MCC originates from neuroendocrine cells of the epidermis and hair follicles, whereas squamous cell carcinoma originates from malignantly transformed epidermal keratinocytes (36), possible mechanisms underlying the associations between MCC and squamous cell carcinoma are speculative. However, both carcinomas may result, at least in part, from chronic exposure to ultraviolet light; alternatively, it is possible that they have a shared epithelial origin in a pluripotent basal cell (37).

The statistically significant increased risk of MCC subsequent to cutaneous malignant melanoma that we and others (4,5) have observed suggests that this increased risk is associated with sun exposure and, possibly, immunosuppression. We also observed an increased risk of cutaneous malignant melanoma subsequent to MCC, although that association was not statistically significant. Both MCC and cutaneous malignant melanoma derive from neural crest cells (5).

Like all register-based studies, this study has some limitations. The possibility of misclassification because of incomplete registration of cases and inaccurate registration of diagnoses is a concern when using register data. However, cancers that are registered in the Danish Cancer Register are histologically confirmed by pathologists. In addition, we included in this study only MCC patients who were diagnosed during or after 1978 when MCC got a unique specific diagnosis code and pathologists were more aware of the diagnosis than they might previously have been. Consequently, MCC diagnoses in the register are likely to be highly specific. Furthermore, pathologists in Denmark are required by law to report all histological findings to the Cancer Register, which should also ensure that registration of MCC is nearly complete (38).

Surveillance bias is a possible explanation for the observed association between MCC and squamous cell carcinoma; the increased risk of a second skin cancer could be explained at least in part by increased vigilance on the part of physicians of patients who already have one skin tumor. However, because we also found an increased risk of non-skin cancers more than 1 year before and after MCC diagnosis but did not find an increased risk of basal cell carcinoma after MCC, it seems unlikely that the observed association between MCC and squamous cell carcinoma was due to increased surveillance.

In conclusion, we found strong associations between MCC and squamous cell carcinoma, chronic lymphocytic leukemia, and cutaneous malignant melanoma, which support one or more shared etiologies for these malignancies. Heightened awareness of associations between MCC and other malignancies may facilitate earlier detection and treatment of MCC and thereby improve the poor prognosis of individuals who are diagnosed with this skin cancer.

References

1. Engels EA, Frisch M, Goedert JJ, Biggar RJ, Miller RW. Merkel cell carcinoma and HIV infection. *Lancet.* 2002;359(9305):497–498.
2. An KP, Ratner D. Merkel cell carcinoma in the setting of HIV infection. *J Am Acad Dermatol.* 2001;45(2):309–312.
3. Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science.* 2008;319(5866):1096–1100.
4. Howard RA, Dores GM, Curtis RE, Anderson WF, Travis LB. Merkel cell carcinoma and multiple primary cancers. *Cancer Epidemiol Biomarkers Prev.* 2006;15(8):1545–1549.
5. Miller RW, Rabkin CS. Merkel cell carcinoma and melanoma: etiological similarities and differences. *Cancer Epidemiol Biomarkers Prev.* 1999;8(2):153–158.
6. Goessling W, McKee PH, Mayer RJ. Merkel cell carcinoma. *J Clin Oncol.* 2002;20(2):588–598.
7. Storm HH. The Danish Cancer Registry, a self-reporting national cancer registration system with elements of active data collection. [Appendix 3(a)] *IARC Sci Publ.* 1991;(95):220–236.
8. *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Version for 2007.* Geneva, Switzerland: World Health Organization; 2006. http://apps.who.int/classifications/apps/icd/icd10online/. Accessed April 7, 2010.
9. Poulsen M. Merkel-cell carcinoma of the skin. *Lancet Oncol.* 2004; 5(10):593–599.
10. Pectasides D, Pectasides M, Economopoulos T. Merkel cell cancer of the skin. *Ann Oncol.* 2006;17(10):1489–1495.
11. Sobin LH, Gospodarowicz MK, Wittekind C, eds. *TNM Classification of Malignant Tumors (UICC International Union Against Cancer).* 7th ed. New York, NY: Wiley-Blackwell; 2009.
12. *International Statistical Classification of Diseases and Related Health Problems, 8th Revision, Danish Version.* http://www.sst.dk/Indberetning%20og%20statistik/Klassifikationer/SKS_download.aspx. "ICD-8 klassifikationen" under "Lukkede klassifikationer."
13. Laursen T, Sørensen H, Fouchard J. 2007. Sundhedsfremmende og smitteforebyggende rådgivning af mennesker, der findes hiv-smittede - Råd til sundhedspersonalet. Sundhedsstyrelsen. [Health promotion and infection prevention counselling for HIV-infected individuals--Guidelines for health professionals]. Danish National Board of Health; 2007. http://www.sst.dk/publ/Publ2007/CFF/HIV/SF_Smit_Raad_Hiv.pdf. Accessed April 9, 2010.
14. Danmarks Statistik. Folketal efter område og tid. [Population figures by area and time]. 2009. http://www.dst.dk/Statistik/nogletal/seneste/Befolkning/Folketal.aspx. Accessed March 1, 2009.
15. Koljonen V, Bohling T, Granhroth G, Tukiainen E. Merkel cell carcinoma: a clinicopathological study of 34 patients. *Eur J Surg Oncol.* 2003;29(7):607–610.
16. Agelli M, Clegg LX. Epidemiology of primary Merkel cell carcinoma in the United States. *J Am Acad Dermatol.* 2003;49(5):832–841.
17. Allen PJ, Bowne WB, Jaques DP, Brennan MF, Busam K, Coit DG. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. *J Clin Oncol.* 2005;23(10):2300–2309.
18. Tai PT, Yu E, Tonita J, Gilchrist J. Merkel cell carcinoma of the skin. *J Cutan Med Surg.* 2000;4(4):186–195.
19. Meeuwissen JA, Bourne RG, Kearsley JH. The importance of postoperative radiation therapy in the treatment of Merkel cell carcinoma. *Int J Radiat Oncol Biol Phys.* 1995;31(2):325–331.
20. Ott MJ, Tanabe KK, Gadd MA, et al. Multimodality management of Merkel cell carcinoma. *Arch Surg.* 1999;134(4):388–392.
21. Allen PJ, Zhang ZF, Coit DG. Surgical management of Merkel cell carcinoma. *Ann Surg.* 1999;229(1):97–105.
22. Albores-Saavedra J, Batich K, Chable-Montero F, Sagy N, Schwartz AM, Henson DE. Merkel cell carcinoma demographics, morphology, and survival based on 3870 cases: a population based study [published online ahead of print July 21, 2009]. *J Cutan Pathol.* PMID: 19638070.
23. Sihto H, Kukko H, Koljonen V, Sankila R, Bohling T, Joensuu H. Clinical factors associated with Merkel cell polyomavirus infection in Merkel cell carcinoma. *J Natl Cancer Inst.* 2009;101(13):938–945.
24. Brenner B, Sulkes A, Rakowsky E, et al. Second neoplasms in patients with Merkel cell carcinoma. *Cancer.* 2001;91(7):1358–1362.
25. Boyle F, Pendlebury S, Bell D. Further insights into the natural history and management of primary cutaneous neuroendocrine (Merkel cell) carcinoma. *Int J Radiat Oncol Biol Phys.* 1995;31(2):315–323.
26. Kean JM, Rao S, Wang M, Garcea RL. Seroepidemiology of human polyomaviruses. *PLoS Pathog.* 2009;5(3):e1000363.
27. Tolstov YL, Pastrana DV, Feng H, et al. Human Merkel cell polyomavirus infection II. MCV is a common human infection that can be detected by conformational capsid epitope immunoassays. *Int J Cancer.* 2009;125(6):1250–1256.
28. Becker JC, Houben R, Ugurel S, Trefzer U, Pfohler C, Schrama D. MC polyomavirus is frequently present in Merkel cell carcinoma of European patients. *J Invest Dermatol.* 2009;129(1):248–250.
29. Kassem A, Technau K, Kurz AK, et al. Merkel cell polyomavirus sequences are frequently detected in nonmelanoma skin cancer of immunosuppressed patients. *Int J Cancer.* 2009;125(2):356–361.
30. Ridd K, Yu S, Bastian BC. The presence of polyomavirus in non-melanoma skin cancer in organ transplant recipients is rare. *J Invest Dermatol.* 2009;129(1):250–252.
31. Busam KJ, Rekthman N, Pulitzer MP, et al. Merkel cell polyomavirus expression in Merkel cell carcinomas and its absence in combined tumors and pulmonary neuroendocrine carcinomas. *Am J Surg Pathol.* 2009; 33(9):1378–1385.
32. Reisinger DM, Shiffer J, Cognetta AB, Chang Y, Moore PS. Lack of evidence for basal or squamous cell carcinoma infection with Merkel cell polyomavirus in immunocompetent patients with Merkel cell carcinoma. *J Am Acad Dermatol.* In press.
33. Shuda M, Arora R, Kwun HJ, et al. Human Merkel cell polyomavirus infection I. MCV T antigen expression in Merkel cell carcinoma, lymphoid tissues and lymphoid tumors. *Int J Cancer.* 2009;125(6):1243–1249.

34. Foschini MP, Eusebi V. Divergent differentiation in endocrine and non-endocrine tumors of the skin. *Semin Diagn Pathol.* 2000;17(2):162–168.
35. Cerroni L, Kerl H. Primary cutaneous neuroendocrine (Merkel cell) carcinoma in association with squamous- and basal-cell carcinoma. *Am J Dermatopathol.* 1997;19(6):610–613.
36. Boukamp P. UV-induced skin cancer: similarities—variations. *J Dtsch Dermatol Ges.* 2005;3(7):493–503.
37. Gomez LG, DiMaio S, Silva EG, Mackay B. Association between neuroendocrine (Merkel cell) carcinoma and squamous carcinoma of the skin. *Am J Surg Pathol.* 1983;7(2):171–177.
38. Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Registry—history, content, quality and use. *Dan Med Bull.* 1997; 44(5):535–539.

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