Merkel cell carcinoma: Current US incidence and projected increases based on changing demographics

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Background: Merkel cell carcinoma (MCC) incidence rates are rising and strongly age-associated, relevant for an aging population.

Objective: Determine MCC incidence in the United States and project incident cases through the year 2025.

Methods: Registry data were obtained from the SEER-18 Database, containing 6600 MCC cases. Age- and sex-adjusted projections were generated using US census data.

Results: During 2000-2013, the number of reported solid cancer cases increased 15%, melanoma cases increased 57%, and MCC cases increased 95%. In 2013, the MCC incidence rate was 0.7 cases/100,000 person-years in the United States, corresponding to 2488 cases/year. MCC incidence increased exponentially with age, from 0.1 to 1.0 to 9.8 (per 100,000 person-years) among age groups 40-44 years, 60-64 years, and ≥85 years, respectively. Due to aging of the Baby Boomer generation, US MCC incident cases are predicted to climb to 2835 cases/year in 2020 and 3284 cases/year in 2025.

Limitations: We assumed that the age-adjusted incidence rate would stabilize, and thus, the number of incident cases we projected might be an underestimate.

Conclusion: An aging population is driving brisk increases in the number of new MCC cases in the United States. This growing impact combined with the rapidly evolving therapeutic landscape warrants expanded awareness of MCC diagnosis and management. (J Am Acad Dermatol 2018;78:457-63.)

Key words: epidemiology; incidence; Merkel cell carcinoma; MCC.

M erkel cell carcinoma (MCC) is a neuroen-docrine skin cancer with high metastatic potential, with one-third to one-half of patients developing recurrence or metastasis. In 2007, annual incidence of MCC in the United States was estimated at 1500 cases/year.[1] Eighty percent of MCCs are caused by a common virus (Merkel cell polyomavirus),[2,3] and the remaining 20% by

extensive ultraviolet (UV)-mediated damage.[4-8] MCCs that are diagnosed at earlier stages have better outcomes, and high dermatologist density has been associated with improved MCC-specific survival, suggesting provider familiarity with MCC might positively affect patient outcomes.[9] For patients with metastatic disease, immunotherapies have been demonstrated to be effective in MCC,[10-12] and emerging evidence suggests that these therapies are most effective if given before any chemotherapy, highlighting the importance of proper up-front systemic therapy.[13] Therefore, updated incidence numbers can allow for better appreciation of the true impact of MCC and, if increasing, proportionally increase its prominence in education for providers, including those in primary care, dermatology, surgery, and medical oncology, with hopes of improving patient outcomes.

From its first description by Toker in 1972,[14] the observed incidence of MCC grew rapidly and this trend was sustained into the new millennium.[15,16] Increases were thought to initially reflect an under appreciation or misdiagnosis of MCC cases that improved in the 1990s with the widespread adoption of CK20 antibody immunohistochemistry. Over the past 10 years, the MCC incidence rates have been reported to continue to rise worldwide: in France,[17] Sweden,[18] Germany,[19] Australia,[20] China,[21] and the United States.[22] However, to our knowledge no estimates of total annual US incidence (number of cases) have been published within the last 5 years. Furthermore, a large population shift is anticipated, with most Baby Boomers passing the 65-year threshold, at which the risk of MCC markedly increases. Indeed, the percentage of Americans >65 years of age is expected to dramatically increase from 13% of the population in 2015 to 20% in 2025.[23] Therefore, we used the Surveillance, Epidemiology, and End Results (SEER) 18 Registry, which captures ~28% of the US population,[24] to estimate current MCC incidence and cross reference these data with US census projections to forecast incidence in 10 years.

MATERIALS AND METHODS
SEER Database

Deidentified national registry data from the SEER-18 Database[25,26] was accessed using SEER*Stat 8.3.2

CAPSULE SUMMARY

- Updated Merkel cell carcinoma (MCC) incidence statistics are needed.

- During 2000-2013, new US MCC cases increased 95% to 2488 diagnoses/year. Further increases are predicted as the population ages.

- The incidence of MCC in 2025 is forecast to be >3000 new cases/year. Given this increasing impact and newly available therapies, more MCC-focused education is needed.

software on February 2017. Incidence data were collected from a SEER-18 rate session. The SEER-18 Registry contains information from registries that are geographically represented across the United States (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Los Angeles, San Jose-Monterey, Rural Georgia, Alaska Native Tumor Registry, Greater California, Greater Georgia, Kentucky, Louisiana, and New Jersey). At the time of database access, data were available for the years 2000-2013. Rates were age and sex adjusted to the 2000 US standard population (19 age groups − Census P25-1130). The data for cases in the research database with known sex and age and tumors with SEER-defined malignant behavior were selected. Data were extracted for MCC (ICD-O-3 hist/ behavior code 8247/3), malignant melanoma (codes 8720/3-8761/3), and SEER-defined site recode B ICD-O-3/WHO 2008 grouping all solid tumors (http://seer.cancer.gov/siterecode).

US Census data

US Census population data for the years 2000-2013 were accessed through a frequency session utilizing SEER*Stat 8.3.2 software (populations, total US 1969-2015 Katrina/Rita adjustment). For the years 2015, 2020, and 2025 US population estimates were downloaded from the 2014 national population projections publicly available at http://www.census.gov.[23]

Statistical analyses

Statistical analyses were performed in SEER*Stat software, and standard errors and confidence intervals (CIs) were generated with the Tiwari et al 2006 modification for CIs.[27] Projected incidences were calculated using 2011-2013 incidence rates for each age and sex bracket (with multiple years allowing for reduced error in incidence rate), and total projected incidence was summed (Supplemental Table I; available at http://www.jaad.org). Graphs were created in GraphPad Prism software.

RESULTS
Trends in MCC incidence rate and reported cases

A total of 6600 cases of MCC were reported to SEER during 2000-2013 (the most recent year for

which data were available at the time of extraction in February 2017). Age- and sex-adjusted incidence rates were calculated and normalized to the 2000 US standard population.

For all solid cancers, there was a significant decrease in the standardized incidence rate between 2000 (429 [95% CI 427.5-430.5] cases/100,000 person-years) and 2013 (379.8 [95% CI 378.6-381.1] cases/100,000 person-years). In contrast, for the most aggressive skin cancers (melanoma and MCC), incidence rates significantly increased. For MCC, the incidence rate rose from 0.5 (95% CI 0.4-0.5) cases/100,000 person-years in 2000 to 0.7 (95% CI 0.7-0.8) cases/100,000 person-years in 2013 (Fig 1, *A*).

Next, we determined changes in the total number of cases reported annually to the SEER-18 Database (28% of US population captured). The number of cases reflects the incidence rate, population at risk, and database capture efficiency. For all solid tumors, there was a modest 15.5% increase in total number of cases reported to SEER-18 (from 313,683 in 2000 to 362,397 in 2013). For MCC, a 95.2% increase was observed (from 334 cases captured by SEER in 2000 to 652 cases in 2013) (Fig 1, *B*); this impressive increase exceeded even the 56.5% increase seen with melanoma (from 13,945 reported cases in 2000 to 21,824 cases in 2013).

Association of demographic factors with MCC

The incidence rate of MCC increases dramatically with age (Fig 2, *A*; n = 6600 MCC cases), and this effect is more pronounced for MCC than for melanoma (Fig 2, *A*; n = 251,437 melanoma cases) or for solid tumors in general (Supplemental Fig 1; available at http://www.jaad.org). Specifically, the MCC incidence rate increases 10-fold between 40-44 years of age (rate 0.1 [95% CI 0-0.1] cases/100,000 person-years) and 60-64 years of age (rate 0.9 [95% CI 0.8-1] cases/100,000 person-years) and 10-fold again between 60-64 years of age and ≥85 years of age (rate 8.3 [95% CI 7.9-8.7] cases/100,000 person-years). This trend has been sustained, and data from 2011-2013 (the most recent years with data available, n = 1778) are consistent: 0.1 cases/100,000 person-years for 40-44 years of age, 1.0/100,000 person-years for 60-64 years of age, and 9.8/100,000 person-years for ≥85 years of age. Unlike most cancers, the rate of MCC continues to substantially rise among individuals in older populations (≥85 years of age); in 2013, the median age of men and women at diagnosis with MCC was 75-79 years. In comparison, the median age for men and women at diagnosis with melanoma was 65-69 years and 60-64 years, respectively. Eighty-four percent of persons with MCC were ≥65 years at diagnosis.

Across all age groups in the United States, the incidence rate of Merkel cell carcinoma is higher among men than women, and this effect is most
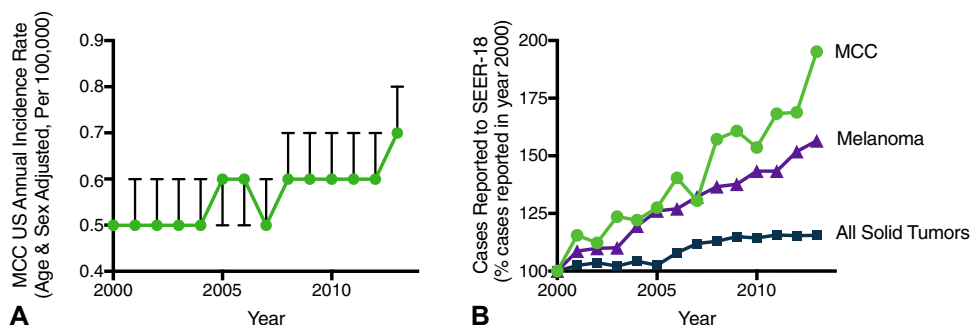
Fig 1. Changes in incidence of MCC compared with incidence of all solid tumors and melanoma, 2000-2013. Data were extracted from the SEER-18 Database, which captures 28% of the US population. **A**, US annual incidence of MCC age and sex adjusted to the 2000 US standard population (cases/100,000 person-years). Bars represent 95% confidence intervals. **B**, Change in number of cases per year reported to SEER-18 (which reflects incidence rate and number of persons at risk in SEER catchment area) normalized to year 2000. During 2000-2013, the total number of solid tumor cases reported (*blue squares*) increased by 15%, the number of melanoma cases (*purple triangles*) increased by 57%, and the number of MCC cases (*green circles*) increased by 95%. *MCC*, Merkel cell carcinoma; *SEER*, Surveillance, Epidemiology, and End Results.

Fig 2. MCC disproportionately affects individuals ≥65 years of age. **A,** Incidence rate by age for MCC (*green circles*, per 100,000 person-years) and melanoma (*purple triangles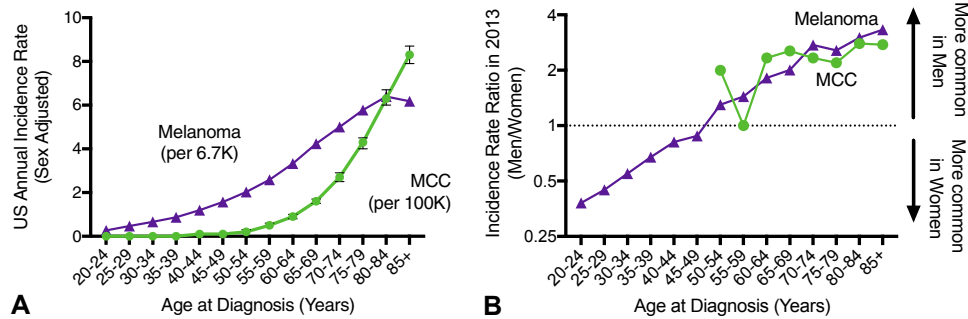*, per 6667 person-years). Unlike melanoma, the incidence rate of MCC increases in individuals ≥85 years of age. Graph includes data from 6600 cases of MCC and 251,437 cases of melanoma (all cases reported to SEER during 2000-2013 with associated age and sex information); 95% confidence intervals are shown. **B,** Relative incidence in men and women by age. Both MCC and melanoma have a strong male predominance in older populations. There are insufficient cases of MCC in persons <50 years of age to determine whether women in the Gen-X and Millennial generations will be at higher MCC risk relative to men, as they are for melanoma. Only 2013 is shown due to rapid changes in melanoma risk for young women. Note that the y-axis has a logarithmic scale. *MCC,* Merkel cell carcinoma.

pronounced among the oldest age groups (Fig 2, *B*). For melanoma, incidence rates are higher among men than women >50 years of age and higher among women than men <50 years of age,[28] which is suspected to be due in part to changing patterns of UV exposure, including indoor tanning.[29] MCC incidence among persons <50 years of age is too low to evaluate whether this trend of increased risk for UV-associated cancer in younger cohorts of women (the Gen-X and Millennial generations) will also hold true for MCC. Approximately two-thirds of MCC cases are currently diagnosed in men, and this proportion was stable between 2000-2013.

UV light is a well-established MCC risk factor.[30] As expected, observed MCC incidence rates were highest among persons more vulnerable to UV light: non-Hispanic white individuals. In the years for which the most recent data is available (2011-2013, n = 1778), the age- and sex-adjusted incidence rate of MCC was higher among non-Hispanic whites (0.8 [95% CI 0.8-0.9] cases/100,000 person-years) than Hispanics (0.3 [95% CI 0.3-0.4] cases/100,000 person-years) and nonwhite, non-Hispanics (0.1 [95% CI 0.1-0.2] cases/100,000 person-years). The percentage of minorities (defined as either Hispanic or nonwhite) presenting with MCC increased significantly between 2000-2002 (7.5%) and 2011-2013 (9.7%, *P* = .045), and increases in MCC incidence rate were seen across all racial and ethnic groups.

Estimates and forecasts for number of MCC incident cases in the United States

The SEER-derived incidence rates were combined with US Census population data to estimate the total US MCC incidence (cases/year) during 2000-2013 and project incidence for 2015, 2020, and 2025. For analyses for the years 2000-2013, we used the incidence rate for each age and sex bracket observed for that particular year. For the years 2015 and later, we used the incidence rate observed for each individual age and sex bracket during 2011-2013 (the most recent years for which data was available; Supplemental Table I). To be conservative (erring towards underestimate), the adjusted incidence rate was not increased but instead held stable; thus, projections reflect only anticipated changes in population demographics.

Based on the US Census reports and the aging Baby Boomer generation, a large and disproportionate increase in the population ≥65 years of age during 2015-2025 is anticipated (Fig 3, *A*).[31] These individuals are predicted to increase from 13% to 20% of the total US population, meaning there will be a large increase in the number of individuals who are at higher risk for MCC.

In 2013, the total number of incident MCC cases in the US (determined using age- and sex-bracketed observed incidence rates and the US Census report) was calculated as 2488 cases/year (Fig 3, *B*). Given the aging of the population and assuming incidence rates for any given age group remain stable, the total incidence of MCC in 2020 is projected to be 2835 cases/year. Given the further increases in populations at higher risk for MCC, the projected annual incidence of MCC in the United States increases to 3284 cases/year in 2025 (Fig 3, *B*).

To determine the approximate accuracy of our approach, we retrospectively performed similar
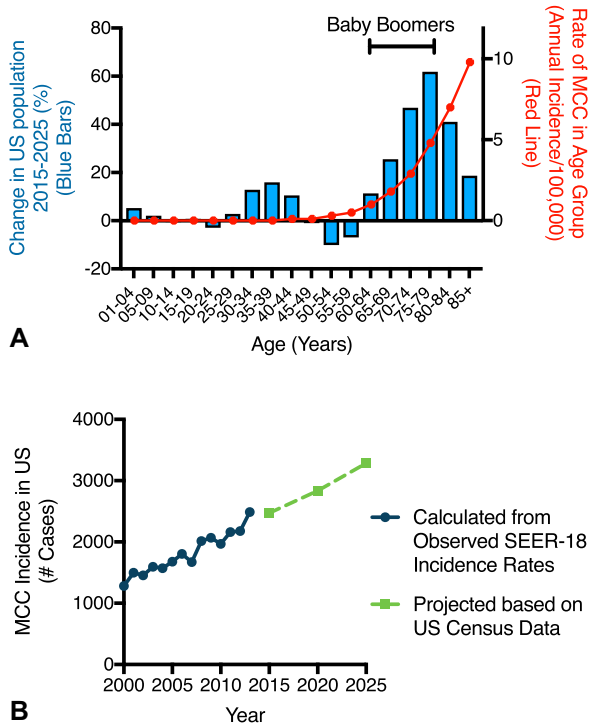
Fig 3. Observed and projected MCC incidence. **A**, Explanation for ongoing brisk rise in MCC incidence. Projected change in US population on the basis of US Census projections (*bars*) with MCC incidence rate per 100,000 person-years from 2011-2013 (*red line*) (most recent years of available data) overlaid. The Baby Boomer generation in 2025 is indicated by the bracket (61-79 years of age in 2025) and account for much of the anticipated rise in MCC incidence. **B**, Observed incidence and projected annual incidence for MCC during 2000-2025, on the basis of SEER-18 data and US Census projections. Estimated incidence in the United States in 2015 is 2472 cases/year and in 2025, 3284 new cases/year. *MCC*, Merkel cell carcinoma.

forecasts (projecting 2008 incidence using 2003 data, and 2013 incidence using 2008 data). When we performed such calculations, the observed numbers of incident cases per year were 9%-13% greater than our projections, indicating that our methods were underestimating true incidence. This was because of increases in the age- and sex-adjusted incidence rate (assumed to be stable for the projections). If one were to instead allow for a 10% increase in incidence rate, the projected annual incidence of MCC would increase to ~3500 cases/year in 2025.

Next, we used the methods of Bashir and Esteve to determine the proportion of the increase in incident cases that was caused by an increased population size versus the proportion that was caused by the aging of the population.[32] For the years 2015 and 2025, we forecast a total increase in incident MCC cases of 812 cases/year (from 2472 cases/year in 2015 to 3284 cases/year in 2025). Of this increase, only 200

cases could be explained by growth in population. The remaining 612 cases are instead caused by the aging of the population, largely the aging of the Baby Boomers.

Ideally, incidence forecasts would effectively control for race and ethnicity. However, because of the relative rarity of MCC in nonwhite populations, forecasts accounting for each racial and ethnic group could not be performed with adequate precision. We did perform forecasts in the largest subset of patients with MCC (non-Hispanic whites) by using race- and ethnicity-specific (as well as age- and sex-specific) incidence rates and population forecasts. By these methods, the number of incident cases in non-Hispanic white individuals in the United States is predicted to be 3077 cases in 2025. Assuming this represents ~90% of total cases of MCC (based on current data from 2011-2013), this brings the total estimate of MCC incident cases in the United States to 3419 cases in 2025, which is roughly concordant with our projected annual incidence of 3284 cases in 2025 cases, as derived earlier.

DISCUSSION

MCC is an aggressive skin cancer that is associated with Merkel cell polyomavirus and sun exposure. The incidence of MCC has risen over the past several decades. Here we report ongoing increases in incidence, with the number of incident cases rising by >95% since the year 2000, which is well above the increase of incident cases of all solid tumors (15%) and even above that of the rapidly increasing cancer type melanoma (57%). We further project incident cases over the next 5 and 10 years, using population projections from the US Census. We estimate current annual incidence at 2500 cases/year in the United States, rising to ~3250 cases/year in 2025 on the basis of the established relationship between age and MCC risk.

MCC particularly affects the elderly; MCC's relationship with age is much more pronounced than melanoma or solid tumors' relationship with age. This relationship is observed despite the fact that infection with Merkel cell polyomavirus often occurs before adulthood.[33-36] Given the critical role that the immune system plays in MCC surveillance, as evidenced by the observation of worse outcomes in immunosuppressed populations,[37] better outcomes in patients with brisk immune responses,[38,39] and excellent responses to immunotherapy among patients with MCC,[10,13] it is plausible that the predilection of MCC for older individuals might reflect diminished immunity in these populations. Indeed, immunosenescence is a well-characterized phenomenon with diminished B-cell and T-cell function and

diminished response to vaccination among older individuals.[40]

Our study had several limitations. Although large, including >6000 patients from a database encompassing >25% of the US population, there might be some geographic differences in incidence not reflected in the available data. Projections are limited to the United States. In future studies, performing similar projections in other US (eg, National Cancer Database or National Program for Cancer Registries) or European and worldwide databases could be considered. For the projections of MCC incidence, we held the rate of MCC incidence for any given age steady despite the observed increases in adjusted-rates over the past decade, and thus, the projected incidence of 3250 cases might be an underestimate of true incidence. Our projections cannot take into account skin tone or changes in sun exposure pattern that might occur across the next 10 years, although changes in these factors are unlikely to have substantial effect in the short term. In addition, we lack immunosuppression data, which can affect risk, although patients with immunosuppression currently represent <10% of those diagnosed with MCC.[30] Finally, our data report on incidence only, not prevalence or mortality.

In conclusion, the incidence of MCC is increasing and will likely continue to rise as the Baby Boomer population enters the higher-risk age groups for MCC. We estimate the rates will exceed 2800 MCC cases/year in 2020 and 3250 cases/year in 2025 in the United States. Because of its high propensity for spread, the need for adjuvant radiation in many cases,[41] and the clear role for early immunotherapy in the metastatic setting, both early detection and optimal management will be critical for improved outcomes. These ongoing increases in MCC incidence strongly advocate for increased specialty-appropriate MCC-specific education to the broad set of providers that care for MCC patients.

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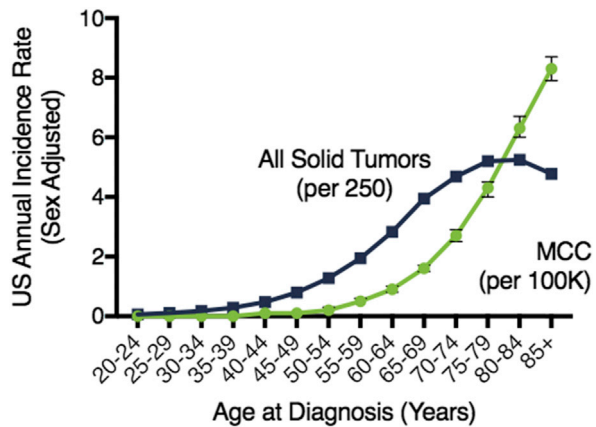
Supplemental Fig 1. MCC disproportionately affects individuals ≥65 years of age as compared with all solid tumors. Incidence rate by age is shown for MCC (*green circles*, per 100,000 person-years) and all solid tumors (*blue squares*, per 250 person-years). In total, 6600 cases of MCC were reported (all cases reported to SEER during 2000-2013 with associated age and sex information). MCC line is identical to Fig 2, *A*; however all solid tumors are now shown instead of melanoma as comparator. *MCC*, Merkel cell carcinoma.

Supplemental Table I. Calculation of predicted number of MCC cases, by age and sex

Sex, age, y	US Census population forecast, in thousands			MCC incidence, per 100,000 person-years	Predicted number MCC cases		
	2015	2020	2025	2011-2013	2015	2020	2025
Men							
0-4	10,211	10,520	10,747	0	0	0	0
5-9	10,448	10,360	10,676	0	0	0	0
10-14	10,513	10,584	10,500	0	0	0	0
15-19	10,796	10,749	10,835	0	0	0	0
20-24	11,678	11,300	11,290	0	0	0	0
25-29	11,447	12,161	11,818	0	0	0	0
30-34	10,906	11,781	12,510	0	0	0	0
35-39	10,181	11,099	11,979	0	0	0	0
40-44	10,025	10,272	11,193	0.1	10	10	11
45-49	10,324	10,010	10,266	0.1	10	10	10
50-54	10,955	10,182	9889	0.3	33	31	30
55-59	10,601	10,651	9929	0.7	74	75	70
60-64	9131	10,147	10,229	1.4	128	142	143
65-69	7612	8567	9556	2.6	198	223	248
70-74	5306	6900	7804	4.1	218	283	320
75-79	3615	4538	5938	7	253	318	416
80-84	2417	2783	3529	12.1	292	337	427
≥85	2181	2432	2802	17.7	386	430	496
Women							
0-4	9755	10,047	10,264	0	0	0	0
5-9	10,015	9914	10,214	0	0	0	0
10-14	10,076	10,150	10,055	0	0	0	0
15-19	10,297	10,299	10,384	0	0	0	0
20-24	11,062	10,759	10,787	0	0	0	0
25-29	11,026	11,561	11,284	0	0	0	0
30-34	10,753	11,387	11,940	0	0	0	0
35-39	10,166	10,961	11,607	0	0	0	0
40-44	10,153	10,296	11,098	0.1	10	10	11
45-49	10,493	10,195	10,347	0.1	10	10	10
50-54	11,356	10,456	10,174	0.2	23	21	20
55-59	11,210	11,228	10,365	0.4	45	45	41
60-64	9962	10,993	11,036	0.7	70	77	77
65-69	8482	9626	10,646	1.1	93	106	117
70-74	6193	7982	9088	1.9	118	152	173
75-79	4512	5574	7216	3.1	140	173	224
80-84	3389	3744	4662	3.6	122	135	168
≥85	4123	4294	4680	5.8	239	249	271

MCC cases are number of incident cases per year in the United States for each of the listed years, in each age and sex category. Total number of predicted incident MCC cases are 2472 in 2015, 2835 in 2020, and 3284 in 2025 (sums in table vary slightly due to rounding).
MCC, Merkel cell carcinoma.