Title: Incidence and survival for Merkel cell carcinoma in Queensland, Australia, 1993-2010

Authors: Danny R. Youlden, BSc[1]; H Peter Soyer, MD FACD[2]; Philippa H Youl, MPH, PhD[1]; Lin Fritschi, MBBS PhD[3]; Peter D Baade, PhD[1].

[1] Cancer Council Queensland, Brisbane, Queensland, Australia.
[2] Dermatology Research Centre, The University of Queensland, School of Medicine, Translational Research Institute, Princess Alexandra Hospital, Brisbane, Queensland, Australia.
[3] Western Australian Institute for Medical Research, The University of Western Australia, Perth, Western Australia, Australia.

Corresponding author: Mr Danny Youlden, Cancer Council Queensland, PO Box 201, Spring Hill, QLD 4004, Australia; E-mail: dannyyoulden@cancerqld.org.au; Telephone: +61-7-36345351.

Author Contributions: Mr Youlden and A/Prof Baade had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design*: All authors. *Analysis and interpretation of data*: Youlden and Baade. *Drafting of the manuscript*: Youlden and Baade. *Critical revision of the manuscript for important intellectual content*: Soyer, Fritschi and Youl. *Statistical analysis*: Youlden. *Obtained funding*: Not applicable. *Administrative, technical, or material support*: Youlden and Soyer. *Study supervision*: Baade.

Funding/Support: Prof Soyer was supported in part by an NHMRC Practitioner Fellowship (APP1020145), Dr Youl was supported by a National Health and Medical Research Council (NHMRC) Early Career Fellowship (ID1054038), Prof Fritschi was supported by fellowships from the NHMRC (ID513706) and the Cancer Council of Western Australia, and A/Prof Baade was supported by an NHMRC Career Development Fellowship (ID1005334).

Role of the Sponsors:

Design and conduct of the study	No
Collection, management, analysis and interpretation of data	No
Preparation, review, or approval of the manuscript	No
Decision to submit the manuscript for publication	No

Financial Disclosure: None reported.

Conflicts of Interest: None reported.

Acknowledgements: The authors wish to thank the staff of the Queensland Cancer Registry who provided the data extract used in this study.

Word counts: Abstract – 302; Body of text – 3,292

Abstract

Importance: Merkel cell carcinoma (MCC) is an uncommon but highly invasive form of skin cancer. The mechanisms that cause MCC are yet to be fully determined.

Objective: To examine the incidence and survival of MCC within a population known to be at high risk of other skin cancers.

Design: Retrospective cohort study.

Setting: Population-based administrative data for MCC collected by the Queensland Cancer Registry, supplemented with detailed histopathological data.

Participants: De-identified records were obtained of all Queensland residents diagnosed with MCC during the period from 1993 to 2010. A sub-sample of histopathology records were reviewed by a senior dermatopathologist to determine the potential for misclassification. A total of 879 eligible cases of MCC were included in the study.

Main Outcomes and Measures: Incidence rates were directly age-standardised to the 2000 United States Standard Population. Trends were examined using JoinPoint software with results expressed in terms of the annual percentage change. The period method was used to calculate five-year relative survival and adjusted hazard ratios were obtained from multivariate Poisson models.

Results: There were 340 cases of MCC diagnosed in Queensland between 2006 and 2010, corresponding to an incidence rate of 1.6/100,000 population. Males (2.5/100,000) had higher incidence than females (0.9/100,000) and rates peaked at 20.7/100,000 for persons aged 80 years and over. The overall incidence of MCC increased by an average of 2.6% per year from 1993 onwards. Relative survival was 41% after 5 years, with significantly better survival

found for those aged under 70 years old at diagnosis (between 56-60%), tumours on the face/ears (51%) and stage I lesions (49%).

Conclusions and Relevance: Incidence rates for MCC in Queensland are at least double any that have been previously published elsewhere in the world. Our findings indicate that a correlation exists between ambient levels of ultraviolet radiation and the incidence of MCC.

Introduction

Merkel cell carcinoma (MCC) is a rare and highly invasive form of neuroendocrine skin cancer that was first described by Toker[1] as trabecular carcinoma in 1972. The neoplasms are composed of small, round blue cells sharing histomorphological and immunohistochemical features with various neuroectodermally derived cells including cutaneous Merkel cells.[2,3] It is currently unclear whether MCCs actually derive from cutaneous Merkel cells or whether they share a common precursor.[2,4,5]

MCCs can be difficult for clinicians to identify because of their nondescript features.[6] However, just recently Jalilian and colleagues[7] described that the four most frequent clinical features were cherry red colour, shiny surface, sharp circumscription and nodular morphology. They also outlined significant dermoscopic features including linear irregular and polymorphous vessels, poorly focused vessels and milky pink areas.[7] Despite the rather characteristic histopathological features, immunohistochemistry staining is required for a definitive diagnosis to differentiate MCC from a broad spectrum of small, round, blue cell neoplasms (e.g. metastasis of an oat cell carcinoma of the lung).[2,5,8] The tumours typically have rapid growth, meaning many patients develop metastatic disease, and recurrence is common despite surgical removal of the primary lesion.[2,8]

MCC is most often diagnosed among elderly Caucasians, with the majority of cases occurring on parts of the body that are more likely to be exposed to the sun, such as the head and neck.[2,5,8] Immunosuppression, which occurs when the body's normal immune responses are inhibited due to medical intervention or disease, is another recognised risk factor,[2,5] and is suggestive of a viral aetiology.[8] The discovery of a polyomavirus (MCPyV)[9] that is present in the majority of MCC tumours has offered new insights into its pathogenesis,[8,10,11] although

much remains unknown. For example, while there is an established association between MCC and ultraviolet (UV) radiation,[8] it is not clear whether UV radiation contributes directly to the development of MCC or if it acts in combination with immunosuppression.[10]

The state of Queensland located in north-eastern Australia has a sub-tropical climate with high levels of UV radiation all year round, combined with a predominantly fair-skinned population and an outdoors lifestyle. Queensland consequently has the highest reported incidence rate of skin cancers worldwide, particularly invasive melanoma.[12-14] The main aim of this paper was to compare the incidence of MCC in Queensland to elsewhere in the world. We also examined incidence trends and investigated differences in survival by key demographic and clinical characteristics.

Methods

Data

Approval for this study was granted by the Griffith University Human Research Ethics Committee (PBH/34/11/HREC). Population-based data on all cases of MCC (defined as ICD-O code C44 and morphology code M8247-3) diagnosed for residents of Queensland between 1993 and 2010 inclusive were obtained from the Queensland Cancer Registry. We excluded cases that were diagnosed prior to 1993 due to the possibility of underreporting of MCC in this period.[15] MCCs were further restricted to those occurring on the skin.

The data available from the Queensland Cancer Registry included demographic information (sex, age at diagnosis, remoteness of residence), diagnostic details (year and anatomical site),

full history of any other cancer diagnoses, and, where relevant, items relating to mortality (time from diagnosis to death and cause of death). Additional clinical information was extracted from histopathology reports where available, including the size of the lesion, lymph node involvement, recurrence, metastases and immunohistochemistry results. Immunosuppression status was categorised as "known to be immunosuppressed" for persons who were a transplant recipient, were HIV positive or who were reported to have another cause of immune suppression. Cases were staged according to the criteria set out by the American Joint Committee on Cancer.[16]

A positive test for cytokeratin 20 (CK20) was considered as confirmation of a diagnosis of MCC, but other variants exist that are CK20 negative.[4,17] To estimate the potential for misclassification of cases that were included in the study, a subsample of approximately 1 in 10 of the histopathology reports for tumours coded to MCC where a negative result was returned for CK20 or where CK20 testing was not recorded were reviewed by a senior dermatopathologist (HPS).

Statistical analyses

Annual incidence rates for the period 1993-2010 and average incidence rates for the latest 5-years (2006-2010) were generated by sex, age group, site and stage at diagnosis. Estimated resident population information used for the rate denominators was obtained from the Australian Bureau of Statistics.[18] To allow for consistency with other similar studies,[15,19] rates were directly age-standardised to the 2000 United States Standard Population.[20] Incidence rate ratios were calculated by simple division, with confidence intervals derived using the method specified by Kegler.[21]

Incidence trends were analysed using Joinpoint regression models (software developed by the National Cancer Institute, version 4.0.4). This approach quantifies the annual percentage change (APC) and specifies any significant changes to the magnitude or direction of the trend (known as a "joinpoint") based on Monte Carlo permutation tests.[22] A maximum of 2 joinpoints were specified in each model, with a minimum of 5 years allowed between joinpoints or between a joinpoint and either end of the data series. Two-sided t-tests were used to determine the statistical significance of the trends ($p<0.05$).

Median survival time, defined as the time from diagnosis to censoring or death, was calculated using the reverse Kaplan-Meier method.[23] Follow-up was censored for subjects who were alive at the end of the study period, as well as at the date of death for those who died from causes other than MCC when examining cause-specific survival. One case was excluded from the survival analysis due to diagnosis on the basis of death certificate only.

Five-year survival was evaluated using the period method,[24] which follows rolling groups of patients within a recent "at risk" window of time and thus has the advantage of producing more up-to-date survival estimates than the more traditional cohort method. In the current study, persons diagnosed with MCC contributed to the survival calculations if they were a prevalent case at some time between 1st January 2006 and 31st December 2010. Estimates for both relative survival and MCC-specific survival were produced. Relative survival was calculated by dividing the observed survival probability for the study group by the expected survival within the Queensland population,[25] matched by age group, sex and year. The Ederer II technique[26] was utilised to compute expected survival.

Differences in survival were assessed by applying multivariate Poisson models to examine excess mortality up to 5 years after diagnosis,[27] with results expressed in terms of adjusted hazard ratios. The dependent variable was the number of deaths, with an offset term for the log of the person years at risk. A range of key demographic and clinical variables were included in the initial model in order to determine which of these characteristics had independent prognostic value. Variables were excluded if there was no evidence ($p>0.25$) of their overall effect on survival (remoteness of residence and level of invasion). Sex, age group, body site, multiple primary cancers, stage at diagnosis and surgical margins were retained in the final model. If the overall effect for a variable was not statistically significant ($p\geq0.05$), then it was deemed that there was no difference in survival even if there appeared to be individual differences in the adjusted hazard ratios between some of the categories.

All of the above results were presented with corresponding 95% confidence intervals (CIs).

Results

Incidence

A total of 903 cases of MCC were diagnosed in Queensland between 1993 and 2010. Of these, 24 were excluded because the lesion occurred on sites other than the skin (mainly on the lips), leaving 879 eligible cases in our cohort.

The distributions for some of the main characteristics of the cohort are given in Table 1. Males accounted for around two-thirds of all cases (68%), with a median age at diagnosis of 75.5 years compared to 78 years for females. Half of the cases were diagnosed at stage I

while 12% already had lymph node metastases (stage III) and a further 15% had distant metastases (stage IV) at the time of diagnosis. Only 1% of patients in the cohort were known to be immune suppressed. More than a third (36%) were diagnosed with another primary cancer apart from MCC, including 10 patients (1%) with chronic lymphocytic leukaemia and 18 patients (2%) with a lymphoma.

The most common site was the face/ears (35%), although the distribution of MCC across the body sites differed by sex ($p < 0.001$). In particular, MCCs on the face/ears occurred more frequently for males (38%) than females (29%), while females were far more likely to have a MCC diagnosed on their lower limbs compared to males (26% and 11%, respectively). Females also had a higher proportion of MCCs that had not yet penetrated beyond the dermal layers of the skin (31% compared to 23% of their male counterparts). No statistically significant differences by sex were found among MCC patients by age group at diagnosis, remoteness of residence, presence of any multiple primary cancers (including second primary MCCs), stage at diagnosis, surgical margins or immunosuppression status.

The average annual age-standardised incidence rate of MCCs in Queensland between 2006 and 2010 was 1.6/100,000 population (95% CI = 1.5-1.8, Supplementary Table 1). Incidence was almost 3 times higher for males (2.5/100,000) compared to females (0.9/100,000). Rates increased rapidly by age, peaking at 20.7/100,000 for persons aged 80 years and over.

Incidence rate trends for MCC in Queensland increased by an average of 2.6% per year (95% CI = +1.1%,+4.2%) between 1993 and 2010, equating to a total rise of 54% over that time interval (Table 2 and Figure 1). Significant and ongoing annual increases were found for males (+2.5% per year), people in the older age groups (70-79 years = +2.3%; 80 years and

over = +3.7%) and tumours that occurred on the head (+3.1%). Significant increases were also observed for tumours that were either stage I (+3.6%) or stages II+ (+2.9%).

Survival

There were 281 deaths (32%) due to MCC within the study group between 1993 and 2010. A further 82 people in the cohort (9%) died from other types of cancers, 213 deaths (24%) were from non-cancer causes, and the remaining 303 persons (34%) were still alive as at the end of 2010. Of the other cancer-related deaths, the main causes were other types of skin cancer and lung cancer (14 deaths each).

The median follow-up time for cases that were prevalent between 2006 and 2010 was 2.8 years (interquartile range = 1.2-6.1 years). Cause-specific survival was 88% (95% CI = 84%-91%) after 1 year and 66% (95% CI = 60%-71%) after 5 years. The corresponding estimates for 1- and 5-year relative survival were 77% (95% CI = 71%-81%) and 41% (95% CI = 34%-48%), respectively.

After adjustment for confounding variables, significant differences in survival remained for age group, site and stage at diagnosis (Table 3 and Figure 2). Specifically, persons who were aged 80 years and over were three times (adjusted HR = 3.0, 95% CI = 1.8-5.1) more likely to die from MCC within 5 years of diagnosis compared to those aged 60-69. Persons with an MCC on either the trunk (adjusted HR = 2.2, 95% CI = 1.2-4.1) or lower limbs (adjusted HR = 1.8, 95% CI = 1.1-3.0) had around double the risk of MCC-related mortality compared to MCC on the face/ears; however, there was no significant difference for lesions on the scalp/neck or upper limbs/shoulders in relation to the face/ears. The risk of MCC-related mortality was also around double for either stage II (adjusted HR = 1.8, 95% CI = 1.1-3.2) or

stage IV tumours (adjusted HR = 2.3, 95% CI = 1.2-4.4) compared to stage I. No significant survival differences were found for sex, remoteness of residence, level of invasion, surgical margins or the presence of multiple primary cancers.

Discussion

This paper contains the first description of the epidemiology for MCC in the state of Queensland, Australia. Several recent population-based studies have been published on the incidence of MCC.[15,19,28-31] Rates in these other studies vary from 0.2/100,000 in Denmark[28] and Finland[31] to 0.8/100,000 in Western Australia.[15] Our results therefore reveal that the incidence rate of MCC in Queensland is at least double that previously reported anywhere else in the world.

Queensland has a predominantly white population living in an area with high levels of ambient UV radiation throughout the year.[32] The higher incidence compared to other countries/regions therefore appears to support a link between exposure to UV radiation and MCC, and is consistent with Agelli and Clegg,[33] who noted a correlation between the UV index and rates of MCC in the United States. In addition, the majority of MCCs in Queensland were found on sun-exposed sites such as the face and ears, scalp and neck, and upper limbs and shoulders, whereas in a less sunny country such as Sweden, a relatively larger percentage of MCCs were observed on the trunk.[29] Our finding of a higher proportion of MCCs occurring on the lower limbs among females is similar to the site distribution of melanoma,[34] another cancer that is strongly related to sun exposure. Similar to Western Australia[15], which also has a high UV index, we found that MCCs occurred more frequently

for males than females. This contrasts with what has been reported in several places in Europe.[28-31]

Average age at diagnosis in other studies ranged from 75-78 years, consistent with the median of 76 years of age in the Queensland cohort. However, a higher proportion (15%) of MCC tumours in Queensland were found to have distant metastases at diagnosis as opposed to 4-8% elsewhere.[15,19,28,30,31]

There was an annual increase of 8% in the incidence of MCC in the United States between 1986-2001,[35] while rates doubled in the Netherlands between 1993-2007[30]. Although the magnitude of the increase in both of these countries has been considerably greater than that observed in Queensland, their incidence rates still remain much lower. The incidence of MCC has stayed fairly stable in Nordic countries since the mid-1990s.[31] At least part of the rapidly increasing incidence rates in the United States during the last two to three decades has been attributed to advances in diagnostic techniques, such as immunohistochemistry, along with greater awareness on the part of medical practitioners.[4,19] This means that a larger proportion of MCC cases are now correctly identified. Changes in the proportion of the population who are immunosuppressed could also have contributed.[30] It is unknown to what extent these factors may have influenced incidence rate trends in Australia, and also why there has been no subsequent change in incidence rates of MCC in countries such as Finland, Sweden, Denmark, Iceland and Norway.[31]

Although the incidence rate of MCC is about forty times lower than invasive melanoma in Queensland,[38] these two types of skin cancers share some epidemiological characteristics. For example, they are more common among males and the elderly. The incidence of both is

continuing to increase sharply among older people, while rates have stabilized among those who are younger.[13] If the role of UV radiation in the development of MCC is found to be similar to that of melanoma, then this stabilising of rates among younger people may provide support for the effectiveness of prevention campaigns.[34]

An analysis of data from Finland reported a similar estimate to ours for 5-year relative survival among males (36%), but a much higher rate for women (69%).[31] Lemos et al[16] calculated five-year relative survival of 54% for a large series of MCC patients from the United States, whereas other studies have estimated relative and cause-specific survival rates of 62% and 64% after 5 years in the Netherlands[30] and Western Australia[15], respectively. While these latter results are similar to our estimate for cause-specific survival, they are substantially higher than the relative survival rate in Queensland.

In most instances, relative survival closely resembles cause-specific survival estimates, as they are designed to measure the same outcome of net survival. One situation where this does not hold true is when the underlying mortality in the cohort is substantially different to that in the general population after accounting for the disease of interest.[39] This could possibly explain why there was a large disparity between the two measures in our study, particularly given that more than half of the deaths within the MCC cohort were due to other causes. Even so, it is still not clear why our estimate of relative survival was substantially lower than some of the other published results, although the higher proportion of cases with metastases at diagnosis in the Queensland cohort may have contributed to these differences to some extent.

Several prognostic factors for MCCs have been identified by other researchers, including sex, site, immune suppression, histopathologic type, growth pattern, and most importantly, the extent of disease at presentation (variously characterised by stage, tumour size or depth and lymphovascular invasion).[5,15,19,40] The influence of MCPyV on survival is controversial,[10,11] but we were not able to measure this in the current study. We found significant differences in the risk of mortality by age, body site and stage at diagnosis after multivariate analysis. One notable difference was that MCCs on the head and neck have been previously associated with a poorer prognosis,[5] which is the opposite of what occurred in Queensland. The reasons for this are not evident.

Most previous studies on Merkel cell carcinoma have involved small samples of less than 200 patients. Therefore, the main strengths of our work were the larger size of the cohort combined with the fact that it represented all cases diagnosed in Queensland, and so was not subject to some of the selection biases that can result from a hospital-based series of patients. Another advantage was the supplementation of standard registry data items with information from histopathology reports.

Only 1% of cases in our data were documented as being immunosuppressed, compared to 6% in a population-based MCC cohort from Western Australia.[15] Information about immunosuppression status was not routinely reported in Queensland, so our result was probably an underestimate of the true proportion. Unfortunately, the small number of immunosuppressed cases also meant that we were unable to assess survival for this subgroup.

While every effort was made to verify legitimate MCC cases, we did not have access to stored biological material (such as specimens and tissue blocks) to assist with this process.

While immunohistochemistry results other than CK20[41] were available to confirm the diagnosis in approximately 80% of the audited histopathology records, the audit revealed that up to 5% of the patients included in this study may have been over-diagnosed. However, this is a conservatively high estimate, and is considered acceptable when taking into account the specific histopathologic diagnostic challenges when dealing with small round blue cell tumours of the skin. Conversely, it is also possible that some cases of MCC were inadvertently excluded due to being incorrectly classified as another type of cancer, but it was not possible to confirm this.

In conclusion, our results establish that the incidence rate of MCC is much higher in Queensland than anywhere else in the world. The central factor behind this undesirable statistic appears to be exposure to UV radiation. While the greater attention placed on melanoma may be warranted given its higher incidence, people diagnosed with MCC have greatly reduced survival expectations. In light of these findings, it is imperative that clinical practice guidelines for the diagnosis and management of MCC, similar to those that already exist for other countries,[42,43] are developed and implemented within Australia as soon as possible.[7] Public awareness campaigns are also required to alert people that melanoma is not the only lethal form of skin cancer. In particular, timely medical opinion should be encouraged for the rapid appearance of a new lesion, with emphasis placed on the importance of people becoming familiar with what is normal for their own skin. It is hoped that these steps will lead to better outcomes for MCC patients into the future.

References

1. Toker C. Trabecular carcinoma of the skin. *Arch Dermatol.* 1972;105(1):107-110.

2. Wang TS, Byrne PJ, Jacobs LK, Taube JM. Merkel cell carcinoma: update and review. *Semin Cutan Med Surg.* 2011;30(1):48-56.

3. Maksimovic S, Baba Y, Lumpkin EA. Neurotransmitters and synaptic components in the Merkel cell-neurite complex, a gentle-touch receptor. *Ann N Y Acad Sci.* 2013;1279:13-21.

4. Pulitzer MP, Amin BD, Busam KJ. Merkel cell carcinoma: review. *Adv Anat Pathol.* 2009;16(3):135-144.

5. Becker JC. Merkel cell carcinoma. *Ann Oncol.* 2010;21(Suppl 7):vii81-85.

6. Taylor G, Mollick DK, Heilman ER. Merkel Cell Carcinoma. In: Rigel DS, Friedman RJ, Dzubow LM, Reintgen DS, Bystryn J, Marks R, eds. *Cancer of the Skin.* Philadelphia: Elsevier Saunders; 2005.

7. Jalilian C, Chamberlain AJ, Haskett M, et al. Clinical and dermoscopic characteristics of Merkel cell carcinoma. *Br J Dermatol.* 2013;169(2):294-297.

8. Nicolaidou E, Mikrova A, Antoniou C, Katsambas AD. Advances in Merkel cell carcinoma pathogenesis and management: a recently discovered virus, a new international consensus staging system and new diagnostic codes. *Br J Dermatol.* 2012;166(1):16-21.

9. Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science.* 2008;319(5866):1096-1100.

10. Schrama D, Ugurel S, Becker JC. Merkel cell carcinoma: recent insights and new treatment options. *Curr Opin Oncol.* 2012;24(2):141-149.

11. Prieto Munoz I, Pardo Masferrer J, Olivera Vegas J, Medina Montalvo MS, Jover Diaz R, Perez Casas AM. Merkel cell carcinoma from 2008 to 2012: reaching a new level of understanding. *Cancer Treat Rev.* 2013;39(5):421-429.

12. Stenbeck KD, Balanda KP, Williams MJ, et al. Patterns of treated non-melanoma skin cancer in Queensland--the region with the highest incidence rates in the world. *Med J Aust.* 1990;153(9):511-515.

13. Coory M, Baade P, Aitken J, Smithers M, McLeod GR, Ring I. Trends for in situ and invasive melanoma in Queensland, Australia, 1982-2002. *Cancer Causes Control.* 2006;17(1):21-27.

14. Leiter U, Garbe C. Epidemiology of melanoma and nonmelanoma skin cancer--the role of sunlight. *Adv Exp Med Biol.* 2008;624:89-103.

15. Girschik J, Thorn K, Beer TW, Heenan PJ, Fritschi L. Merkel cell carcinoma in Western Australia: a population-based study of incidence and survival. *Br J Dermatol.* 2011;165(5):1051-1057.

16. Lemos BD, Storer BE, Iyer JG, et al. Pathologic nodal evaluation improves prognostic accuracy in Merkel cell carcinoma: analysis of 5823 cases as the basis of the first consensus staging system. *J Am Acad Dermatol.* 2010;63(5):751-761.

17. Calder KB, Coplowitz S, Schlauder S, Morgan MB. A case series and immunophenotypic analysis of CK20-/CK7+ primary neuroendocrine carcinoma of the skin. *J Cutan Pathol.* 2007;34(12):918-923.

18. Australian Bureau of Statistics. *Australian Demographic Statistics, Dec 2011: 2011 Census Edition — Preliminary.* Canberra: ABS; 2012. ABS Cat. No. 3101.0.

19. 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. *J Cutan Pathol.* 2010;37(1):20-27.

20. United States Census Bureau. US Standard Population, 1940-2000. Available from http://seer.cancer.gov/stdpopulations/stdpop.19ages.html. Accessed 3 June 2013.

21. Kegler SR. Applying the compound Poisson process model to the reporting of injury-related mortality rates. *Epidemiol Perspect Innov.* 2007;4:1.

22. Kim H, Fay M, Feuer E, Midthune D. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med.* 2000;19:335-351.

23. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials.* 1996;17(4):343-346.

24. Brenner H, Gefeller O, Hakulinen T. Period analysis for 'up-to-date' cancer survival data: theory, empirical evaluation, computation realisation and applications. *Eur J Cancer.* 2004;40:326-335.

25. Australian Bureau of Statistics. *Deaths, Australia, 2011.* Canberra: ABS; 2012. ABS Cat. No. 3302.0.

26. Ederer F, Axtell LM, Cutler SJ. The relative survival rate: a statistical methodology. *NCI Monogr.* 1961;6:101-121.

27. Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. *Stat Med.* 2004;23(1):51-64.

28. Kaae J, Hansen AV, Biggar RJ, et al. Merkel cell carcinoma: incidence, mortality, and risk of other cancers. *J Natl Cancer Inst.* 2010;102(11):793-801.

29. Hussain SK, Sundquist J, Hemminki K. Incidence trends of squamous cell and rare skin cancers in the Swedish national cancer registry point to calendar year and age-dependent increases. *J Invest Dermatol.* 2010;130(5):1323-1328.

30. Reichgelt BA, Visser O. Epidemiology and survival of Merkel cell carcinoma in the Netherlands. A population-based study of 808 cases in 1993-2007. *Eur J Cancer.* 2011;47(4):579-585.

31. Kukko H, Bohling T, Koljonen V, et al. Merkel cell carcinoma - a population-based epidemiological study in Finland with a clinical series of 181 cases. *Eur J Cancer.* 2012;48(5):737-742.

32. Neale RE, Hamilton AR, Janda M, Gies P, Green AC. Seasonal variation in measured solar ultraviolet radiation exposure of adults in subtropical Australia. *Photochem Photobiol*. 2010;86(2):445-448.

33. Agelli M, Clegg LX. Epidemiology of primary Merkel cell carcinoma in the United States. *J Am Acad Dermatol.* 2003;49(5):832-841.

34. Youl PH, Youlden DR, Baade PD. Changes in the site distribution of common melanoma subtypes in Queensland, Australia over time: implications for public health campaigns. *Br J Dermatol.* 2013;168(1):136-144.

35. Hodgson NC. Merkel cell carcinoma: changing incidence trends. *J Surg Oncol.* 2005;89(1):1-4.

36. Queensland Cancer Registry, Cancer Council Queensland, Queensland Health. *Cancer in Queensland, 1982-2010.* Brisbane: CCQ; 2013.

37. Sarfati D, Blakely T, Pearce N. Measuring cancer survival in populations: relative survival vs cancer-specific survival. *Int J Epidemiol.* 2010;39(2):598-610.

38. Andea AA, Coit DG, Amin B, Busam KJ. Merkel cell carcinoma: histologic features and prognosis. *Cancer.* 2008;113(9):2549-2558.

39. Argenyi ZB. Neural and Neuroendocrine Neoplasms (Other than Neurofibromatosis). In: Bolognia JL, Jorizzo JL, Schaffer JV, eds. *Dermatology, third edition*. Philadelphia: Elsevier Saunders; 2012.

40. Miller SJ, Alam M, Andersen J, et al. Merkel cell carcinoma. *J Natl Compr Canc Netw.* 2009;7(3):322-332.

41. Boccara O, Girard C, Mortier L, Bens G, Saiag P, Guillot B. Guidelines for the diagnosis and treatment of Merkel cell carcinoma - Cutaneous Oncology Group of the French Society of Dermatology. *Eur J Dermatol.* 2012;22(3):375-379.

42. Australian Bureau of Statistics. *Statistical Geography Volume 1 - Australian Standard Geographical Classification (ASGC).* Canberra: ABS; 2006.

Table 1. Characteristics of persons diagnosed with Merkel cell carcinoma by sex, Queensland, 1993-2010

	Males		Females		Persons	
Characteristic	**n**	**Col %**	**n**	**Col %**	**n**	**Col %**
TOTAL	**602**	**100.0**	**277**	**100.0**	**879**	**100.0**
Age group at diagnosis	Chi-square = 6.16; df = 4; p = 0.187					
0-39	6	1.0	1	0.4	7	0.8
40-59	59	9.8	18	6.5	77	8.8
60-69	118	19.6	47	17.0	165	18.8
70-79	204	33.9	94	33.9	298	33.9
80+	215	35.7	117	42.2	332	37.8
Body site	Chi-square = 41.35; df = 5; p < 0.001					
Face/Ears	228	37.9	79	28.5	307	35.0
Scalp/Neck	77	12.8	24	8.7	101	11.5
Trunk	47	7.8	25	9.0	72	8.2
Upper limbs/shoulders	75	12.5	44	15.9	119	13.5
Lower limbs	66	11.0	72	26.0	138	15.7
Not specified	109	18.1	33	11.9	142	16.2
Remoteness of residence[a]	Chi-square = 5.60; df = 4; p = 0.231					
Major city	337	56.0	157	56.7	494	56.2
Inner regional	146	24.3	58	20.9	204	23.2
Outer regional	89	14.8	40	14.4	129	14.7
Remote/very remote	28	4.7	18	6.5	46	5.2
Not stated	2	0.3	4	1.4	6	0.7
Multiple primary cancers (all types)	Chi-square = 5.57; df = 2; p = 0.062					
No	370	61.5	192	69.3	562	63.9
Yes – previous years	155	25.7	53	19.1	208	23.7
Yes – same/subsequent years	77	12.8	32	11.6	109	12.4
Stage at diagnosis[b]	Chi-square = 4.42; df = 4; p = 0.352					
Stage I	295	49.0	143	51.6	438	49.8
Stage II	55	9.1	34	12.3	89	10.1
Stage III	71	11.8	31	11.2	102	11.6
Stage IV	101	16.8	35	12.6	136	15.5
Unknown	80	13.3	34	12.3	114	13.0
Level of invasion[c]	Chi-square = 6.31; df = 2; p = 0.043					
Dermis	141	23.4	87	31.4	228	25.9
Dermis/subcutaneous	243	40.4	101	36.5	344	39.1
Not stated	218	36.2	89	32.1	307	34.9
Surgical margins	Chi-square = 2.28; df = 2; p = 0.320					
Satisfactory (clear)	278	46.2	143	51.6	421	47.9
Unsatisfactory (not clear)	123	20.4	52	18.8	175	19.9
Not stated	201	33.4	82	29.6	283	32.2
Immune status[d]	Chi-square = 0.02; df = 1; p = 0.893					
Known to be immune suppressed	8	1.3	4	1.4	12	1.4
Not known to be immune suppressed	594	98.7	273	98.6	867	98.6

Abbreviations/symbols: n = number of cases; df = degrees of freedom.

Notes: a. Remoteness of residence based on the Australian Standard Geographical Classification Remoteness Areas.[44]

b. Stage at diagnosis defined according to the criteria set out by the American Joint Committee on Cancer.[16]

c. Dermis category may include epidermal involvement. Dermis/subcutaneous category includes cases where the tumour extended beyond the dermal layer.

d. Immune status was categorised as suppressed for persons who were known to be a transplant recipient, HIV positive or who were reported to have another cause of immune suppression.

Table 2. Annual percentage change (APC)[a] in the incidence rates[b] of Merkel cell carcinoma by selected characteristics, Queensland, 1993-2010

Characteristic	n	APC (95% CI)[c]	p-value
TOTAL	879	**+2.6 (+1.1,+4.1)**	**0.002**
Sex			
Males	602	**+2.5 (+0.9,+4.1)**	**0.004**
Females	277	+2.1 (-0.7,+5.1)	0.132
Age group at diagnosis			
0-59	84	-1.4 (-5.8,+3.2)	0.515
60-69	165	+2.0 (-1.1,+5.1)	0.195
70-79	298	**+2.3 (+0.1,+4.6)**	**0.039**
80+	332	**+3.7 (+1.0,+6.4)**	**0.009**
Body site[d]			
Head	408	**+3.1 (+1.1,+5.2)**	**0.005**
Other	329	+1.3 (-1.1,+3.8)	0.259
Not specified	142	+2.2 (-1.5,+6.1)	0.225
Stage at diagnosis[e]			
Stages I	438	**+3.6 (+1.1,+6.2)**	**0.008**
Stages II+	327	**+2.9 (+0.2,+5.6)**	**0.036**
Unknown	114	-2.9 (-6.2,+0.5)	0.086

Abbreviations: APC = annual percentage change; 95% CI = 95% confidence interval.

Notes: a. Calculated using JoinPoint regression.

b. Rates were directly age-standardised to the 2000 United States Standard Population.[20]

c. Trends shown in bold were statistically significant.

d. Head includes the face, ears, scalp and neck. Other body site includes the trunk, upper limbs, shoulders and lower limbs.

e. Stage at diagnosis defined according to the criteria set out by the American Joint Committee on Cancer.[16]

Table 3. Five-year relative survival[a] and adjusted hazard ratios for Merkel cell carcinoma by selected characteristics, Queensland, 2006-2010

Characteristic	n[b]	Five-year RS[a] (95% CI)	Adjusted HR (95% CI)	p
TOTAL	489	41.3 (34.4-48.4)		
Sex	Chi-square = 1.59; df = 1; p = 0.208			
Males	338	38.2 (30.0-46.8)	1.00 [g]	
Females	151	48.1 (35.5-60.4)	0.77 (0.51-1.16)	0.208
Age group at diagnosis	Chi-square = 29.03; df = 3; p < 0.001			
0-59	47	56.5 (35.8-73.1)	0.75 (0.36-1.58)	0.454
60-69	95	59.9 (43.5-73.6)	1.00 [g]	
70-79	165	43.2 (32.0-54.4)	1.42 (0.83-2.44)	0.201
80+	182	24.6 (14.0-38.3)	3.00 (1.76-5.10)	<0.001
Body site	Chi-square = 12.00; df = 5; p = 0.035			
Face/ears	186	51.3 (38.5-64.0)	1.00 [g]	
Scalp/neck	47	45.2 (19.9-73.2)	1.02 (0.52-2.00)	0.955
Trunk	41	24.8 (10.2-43.6)	2.19 (1.16-4.13)	0.016
Upper limbs/shoulders	63	38.1 (20.4-57.5)	1.40 (0.77-2.53)	0.271
Lower limbs	76	33.3 (20.0-48.3)	1.81 (1.08-3.00)	0.022
Not specified	76	33.2 (17.9-50.3)	0.90 (0.43-1.88)	0.780
Remoteness of residence[c,d]				
Major city	273	38.6 (29.7-48.1)	(c)	
Inner regional	119	51.3 (35.5-67.0)	(c)	
Other/Unknown	97	36.8 (23.6-50.9)	(c)	
Multiple primary cancers (all types)	Chi-square = 4.06; df = 2; p = 0.131			
No	316	46.2 (37.1-55.2)	1.00 [g]	
Yes – previous years	122	29.8 (17.4-44.3)	1.50 (1.01-2.23)	0.045
Yes – same/subsequent years	51	37.0 (20.0-55.8)	1.22 (0.69-2.17)	0.500
Stage at diagnosis[e]	Chi-square = 9.91; df = 4; p = 0.042			
Stage I	266	48.8 (38.8-58.7)	1.00 [g]	
Stage II	53	26.2 (8.9-50.1)	1.83 (1.06-3.15)	0.030
Stage III	53	41.4 (21.7-63.1)	1.55 (0.87-2.74)	0.135
Stage IV	70	25.4 (13.4-39.8)	2.29 (1.21-4.36)	0.011
Unknown	47	43.1 (19.5-68.7)	1.01 (0.50-2.06)	0.977
Level of invasion[c,f]				
Dermis	141	45.5 (31.5-59.9)	(c)	
Subcutaneous	204	41.9 (31.7-52.5)	(c)	
Not stated	144	37.2 (25.3-49.7)	(c)	
Surgical margins	Chi-square = 3.77; df = 2; p = 0.152			
Satisfactory (clear)	272	47.5 (37.7-57.3)	1.00 [g]	
Unsatisfactory (not clear)	86	39.9 (24.1-57.1)	1.29 (0.81-2.04)	0.277
Not stated	131	30.1 (18.9-42.5)	1.68 (0.96-2.94)	0.068

Abbreviations: RS = relative survival; HR = hazard ratio; 95% CI = 95% confidence interval.

Notes:
a. Survival calculated using the period method for persons who were at risk of mortality due to Merkel cell carcinoma between 1 Jan 2006 to 31 Dec 2010.
b. The number of persons who were eligible to contribute to the 5-year relative survival calculations.
c. Remoteness of residence and level of invasion were excluded from the final multivariate Poisson model for calculating the hazard ratios because the overall effect for these variables was p>0.25.
d. Remoteness of residence based on the Australian Standard Geographical Classification Remoteness Areas.[44]
e. Stage at diagnosis defined according to the criteria set out by the American Joint Committee on Cancer.[16]
f. Dermis category may include epidermal involvement. Dermis/subcutaneous category includes cases where the tumour extended beyond the dermal layer.
g. Reference category.

Figure 1. Incidence rate trends for Merkel cell carcinoma by sex, age group at diagnosis, body site and stage at diagnosis, Queensland, 1993-2010. Trends calculated using JoinPoint regression, based on rates that were directly age-standardised to the 2000 United States Standard Population.[20] Head includes the face, ears, scalp and neck. Other body site includes the trunk, upper limbs, shoulders and lower limbs. Stage at diagnosis defined according to the criteria set out by the American Joint Committee on Cancer.[16]

Figure 2. Unadjusted relative survival curves for Merkel cell carcinoma by sex, age group at diagnosis, body site and stage at diagnosis, Queensland, 2006-2010. Survival calculated using the period method for persons who were at risk of mortality due to Merkel cell carcinoma between 1 Jan 2006 to 31 Dec 2010. Stage at diagnosis defined according to the criteria set out by the American Joint Committee on Cancer.[16]