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Incidence and Mortality of Conjunctival Melanoma in Australia (1982 to 2014)

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PURPOSE. The purpose of this study was to estimate the incidence and mortality of conjunctival melanoma in Australia from 1982 to 2014.

METHODS. De-identified unit data for all cases of ocular melanoma were extracted from the Australian Cancer Database from 1982 to 2014. Conjunctival melanoma cases were extracted, and the incidence and mortality were analyzed. Incidence rates were age-standardized against the 2001 Australian Standard Population. Mortality was assessed using log-rank and Cox regression.

RESULTS. From 1982 to 2014, there were 299 cases of conjunctival melanoma. The age-standardized incidence rate was 0.48 (95% confidence interval [CI] = 0.41 to 0.54) per million per year. Women (0.52, 95% CI = 0.42 to 0.62) had a higher incidence than men (0.42, 95% CI = 0.33 to 0.51). The incidence of conjunctival melanoma increased in men (+1.46%) and significantly women (+1.41%, $P = 0.023$) over the study period. The mean 5-, 10-, and 15-year disease-specific survival were 90%, 82%, and 80%, respectively, during the 33-year interval. Comparisons of survival among age, sex, and state revealed no significant differences when tested using log-rank or Cox regression.

CONCLUSIONS. In conclusion, we found an increase in the rate of conjunctival melanoma diagnoses in Australia from 1982 to 2014. Over the same period, disease survival remained unchanged at a mean of 90%.

Keywords: conjunctival melanoma, Australia, incidence, mortality, ocular melanoma

Conjunctival melanoma (CJM) is a rare form of mucosal melanoma and makes up around 5% to 7% of all ocular melanomas.¹⁻³ Historical data have shown that the condition affects approximately 0.8 and 0.4 men and women per million per year in Australia, respectively,¹ and is rarer than uveal melanoma.⁴ This rate is similar to Europe,⁵ and higher than that of the United States.⁶ Similar to other forms of melanoma, Caucasian ethnicity is associated with increased risk of disease development.⁷ As of the 2021 census, of the Australian population of approximately 25 million persons, 46% had North-West European, 30% had Australian (majority Anglo-Celtic ancestry), 11% had Southern and Eastern European, 10% had East Asian, 7% had Southern and Central Asian, 3% had Aboriginal or Torres Strait Islander, and 6% had other ancestries listed. Note, up to two ancestries can be reported per person.⁸ In contrast, genetically similar areas, such as Europe and approximately half of North America, contained approximately 745⁹ and approximately 369^{10,11} million persons, respectively, in the same period. Local recurrence rates post-therapy are relatively high,¹² with a high 5-

year survival.⁵ Unlike the most common ocular melanoma, uveal melanoma,¹³ ultraviolet radiation appears to be a clear driver of DNA damage^{14,15} in most CJM cases. Given the incidence of the UV driven cutaneous melanoma, mostly by improved recognition of in situ cases, has increased in the last few decades¹⁶ and as the last review of CJM in Australia was performed in the early 2000s,¹ we aimed to examine changes in the incidence and mortality of CJM in Australia from 1982 to 2014.

MATERIALS AND METHODS

Data Collection

De-identified unit-record data from 1982 to 2015 was extracted from the state cancer registries (Australian Cancer Database) and linked through the Australian Institute of Health and Welfare (www.aihw.gov.au). International Classification of Disease for Oncology version 3 (ICD-O-3.1 and ICD-O-3),¹⁷ codes for melanoma (8720-8790) and site



(C69.0–C69.9) were used to obtain unit data with the following information: state, sex, country of birth, year of diagnosis, age at diagnosis (rounded down to nearest whole year), ICD-O-3 topography, ICD-O-3.1 histology, vital status at 31/12/15, cause of death, and survival time. Diagnoses data for New South Wales was missing in the year 2015, and thus for assessment of incidence, only years 1982 to 2014 were used. However, data were available from 1982 to 2015 for all other states and territories. Thus, this date was used for survival analysis. Last, data from New South Wales and the Australian Capital Territory were combined to obfuscate values $n \leq 5$ as per the request of the data custodians.

Data Analysis

Incidence. Analysis was performed as per Beasley et al., 2021.⁴ Briefly, Australian Census data and annual population data were downloaded from the Australian Bureau of Statistics (<https://www.abs.gov.au/>) from 1981 to 2015. These data were used to calculate direct age-standardized incidence rates (ASRs), standardized to the 2001 Australian standard population. Incidence was plot-

ted using R (v4.0.4). Indirect age-standardized incidence ratios (SIRs) were further calculated for individual states (compared to Australia) given the low case numbers. Changes in incidence from 1982 to 2014 were calculated using the JoinPoint Regression Program (version 4.8.0.1, April 2020; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute).¹⁸ The change in incidence in these segments was reported as the annual percent change (APC). A significant change in the APC was reported if $P \leq 0.05$. A map of Australia was generated using *cartopy* (version 0.18.0), *geopandas* (version 0.9.0), and *matplotlib* in Python (version 3.8.10). Calculated SIRs were plotted to each state or territory except for the Northern Territory. The 2017 to 2018 population was overlaid to give readers estimates of populous areas.

Mortality. The 5-, 10-, and 15-year disease specific survival was calculated¹⁹ using survival time between date of diagnosis and date of death encoded to CJM, or censored in the case of unrelated death. Disease-specific survival was compared between states and sex using log rank in R with the survival package (version 3.2-3) and survminer (version 0.4.8). Univariate and multivariate Cox proportional-hazards

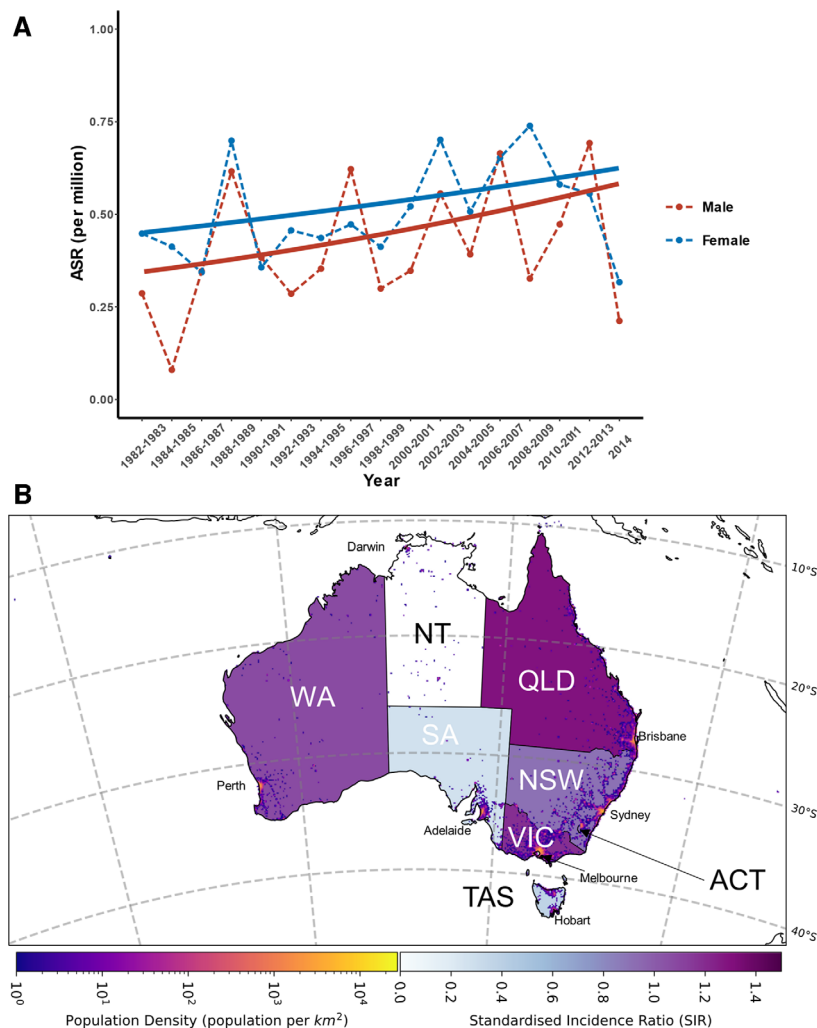


FIGURE 1. (A) Incidence of conjunctival melanoma. Age-standardized incidence rates (ASRs) from 1982 to 2014 per million population standardized to the 2001 Australian standard population with trendline. Men indicated by *red*, and women by *blue*. **(B)** Map of Australia with annotations of state/capital/population density with the standardized incidence ratios (SIRs) of conjunctival melanoma, shown by *blue/purple* gradient.

model was used to measure subgroup hazard ratios (HRs) to determine predictors of survival, including state, sex, and age in R.^{20,21} The cumulative survival was calculated using *cmprsk* (version 2.2-11) in R. Last, relative survival was performed using *relsurv* (version 2.2-5) in R²² with the “ederer2” method using population mortality data obtained for the Australian population from the Human Mortality Database (1 × 1).²³

RESULTS

Population Characteristics

A total of 5087 cases of ocular melanoma were extracted from the Australian Cancer Database from 1982 to 2014. Of these, 299 (5.9%) were classified as CJM. More female patients (*n* = 174, 58.2%) were diagnosed with CJM than male patients (*n* = 125, 41.8%). The mean (±SD) and median age of diagnosis was 60 (±19.6) and 64 years (range = 6–97),

respectively. Of the 299 cases of CJM, 218 (72.9%) were born in Australia, followed by 28 (9.4%) in North-West Europe, 10 (3.3%) in Southern and Eastern Europe, and 43 (14.4%) classified as “other.” The majority of cases were from the most populous Australian state of New South Wales and Australian Capital Territory (NSW + ACT, *n* = 97, 32.4%), followed by Victoria (VIC; *n* = 91, 30.4%), Queensland (QLD; *n* = 71, 23.7%), Western Australia (WA; *n* = 31, 10.4%), South Australia (SA; *n* = 7, 2.3%), and Tasmania (TAS; *n* = 3, 1%). The Northern Territory (NT) had no cases encoded to CJM.

Incidence Rates

The average ASR of CJM was 0.48 (95% confidence interval [CI] = 0.41 to 0.54) per million per year. Female patients had a higher ASR at 0.52 (95% CI = 0.42 to 0.62) per million per year when compared to males whose ASR was 0.42 (95% CI = 0.33 to 0.51). Join-point analysis of the ASR in female patients revealed a significant (*P* = 0.023) increase in the

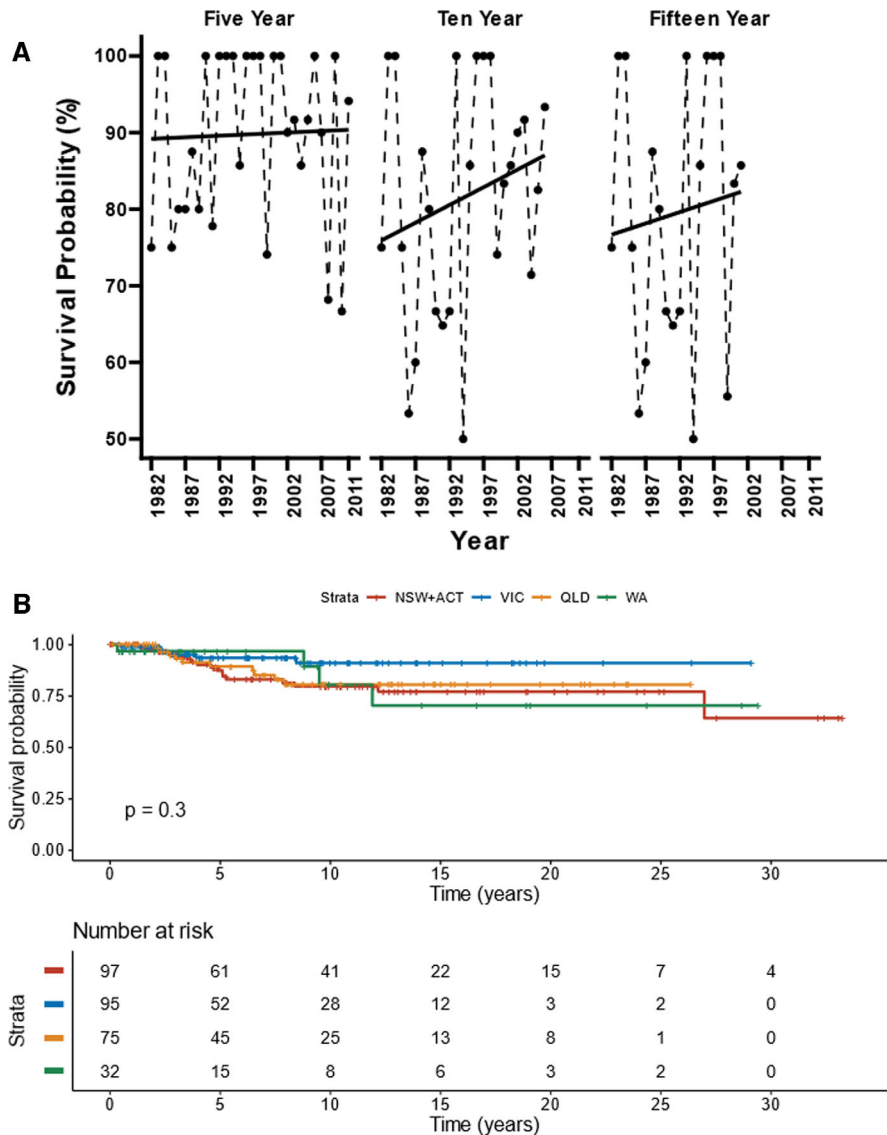


FIGURE 2. Overall survival of conjunctival melanoma. (A) The 5-, 10-, and 15-year disease-specific survival for conjunctival melanoma. (B) Kaplan-Meier (log rank *P* value indicated) estimates for New South Wales plus the Australian Capital Territory (NSW + ACT, *n* = 97, red), Victoria (VIC; *n* = 95, blue), Queensland (QLD; *n* = 75, orange), and Western Australia (WA; *n* = 32, green).

TABLE. Subgroup Analysis

Variables	n	Univariate HR (95% CI, P Value)	Multivariate HR (95% CI, P Value)
State			
NSW + ACT	97	1	1
QLD	75	0.87 (0.39–1.90, <i>P</i> = 0.721)	0.88 (0.40–1.94, <i>P</i> = 0.758)
SA	10	1.59 (0.21–12.18, <i>P</i> = 0.657)	1.46 (0.19–11.23, <i>P</i> = 0.717)
TAS	4	1.73 (0.23–13.04, <i>P</i> = 0.597)	1.81 (0.24–13.95, <i>P</i> = 0.568)
VIC	95	0.42 (0.17–1.07, <i>P</i> = 0.069)	0.41 (0.16–1.05, <i>P</i> = 0.064)
WA	32	0.90 (0.30–2.66, <i>P</i> = 0.842)	0.83 (0.28–2.50, <i>P</i> = 0.744)
Age, y			
<60	127	1	1
≥60	186	1.41 (0.74–2.69, <i>P</i> = 0.297)	1.42 (0.74–2.74, <i>P</i> = 0.288)
Sex			
Female	181	1	1
Male	132	1.11 (0.59–2.09, <i>P</i> = 0.749)	1.20 (0.63–2.28, <i>P</i> = 0.583)

incidence from 1982 to 2014 (APC = +1.41%, 95% CI = 0.2 to 2.6), whereas male patients had a nonsignificant increase (APC = +1.46, 95% CI = −0.9 to 3.9). No breakpoints were identified in the data (Fig. 1A). Generally, male and female patients had similar rates of CJM until ages 65+ years where female patients had a higher ASR (Supplementary Fig. S1).

Between the states and territories, Queensland had the highest SIR of 1.3 (95% CI = 1.03 to 1.68), followed by Victoria (1.2, 95% CI = 0.97 to 1.47), Western Australia (1.09, 95% CI = 0.73 to 1.56), New South Wales plus Australian Capital Territory (0.91, 95% CI = 0.74 to 1.11), Tasmania (0.38, 95% CI = 0.08 to 1.11), and South Australia (0.27, 95% CI = 0.11 to 0.56) (Fig. 1B). No cases were reported in the Northern Territory.

Mortality

From 1982 to 2015, there were 313 cases of CJM. Over the last 34 years, 133 patients died with 39 (29%) of these cases dying due to CJM. Of these 133 deaths, 80 women died, with 22 (28%) dying due to CJM, and 54 men died, with 17 (31%) dying due to CJM. The 5-, 10-, and 15-year disease-specific survivals was relatively stable at an average of 90% (95% CI = 86% to 94%), 82% (95% CI = 76% to 88%), and 80% (95% CI = 72% to 87%), respectively. The AAPCs showed nonsignificant increases of +0.04% (95% CI = −0.5% to 0.6%), +0.7% (95% CI = −0.9% to 2.3%), and +0.3% (95% CI = −2.8% to 3.1%), respectively (Fig. 2A). There was no significant difference in survival between states (New South Wales plus Australian Capital Territory, Victoria, Queensland, and Western Australia) via Cox regression or log rank (Fig. 2B, see the Table). Cumulative survival indicated that death to other causes Australia-wide exceeded death to CJM (Supplementary Fig. S2a). Separating this into states revealed that until 12 years, death to CJM and other causes were similar, and only after the probability of death to other causes overtakes CJM in New South Wales plus Australian Capital Territory. In Western Australia, the probability of death to CJM overtakes other causes after around 12 years. However, the cumulative probability of death from any cause is lower than the other measured states (Supplementary Fig. S2b). No difference was observed between males and female patients in disease-specific survival (Supplementary Fig. S3). However, assessing survival using the Ederer II method (relative survival) reveals sex-specific differences 15 years where men begin to increase in relative survival and women decrease (Supplementary Fig. S4a). Similarly, separating relative survival into

states reveals both New South Wales plus Australian Capital Territory and Queensland have median survival rates of 25.1 and 21.8 years, respectively. Last, the relative survival of those in Western Australia begins to increase dramatically after 15 years (0.852, 95% CI = 0.573 to 1.73) to 1.166 (95% CI = 0.784 to 1.73), and 1.62 (95% CI = 1.104 to 2.44) at 20 and 25 years, respectively (Supplementary Fig. S4b).

DISCUSSION

Conjunctival melanoma is a rare disease of the eye that has gradually increased in rate since the inception of the Australian Cancer Database in 1982. Women had a higher ASR of CJM compared to men. Interestingly, this differs with other studies showing men having higher ASRs,^{1,3,5} although the differences are generally minimal in ours and other studies. This contrasts with uveal melanoma and cutaneous melanoma where men have a higher incidence.^{4,16} In comparison, mucosal melanomas are indeed more common in women, however, this is primarily driven by genital tract melanomas.³ Similarly, although the increase in incidence has been seen in some studies, others have reported stable changes over time.²⁴

Interestingly, whereas the conjunctiva is a mucosal membrane and CJM could be broadly classified as mucosal, they carry distinct genetic alterations and have been shown to harbor a high frequency of the UVR-associated single base substitution signature 7 (SBS7).¹⁴ Given that CJM may be primarily driven by UV radiation, it was unsurprising that Queensland had the highest SIR of all states in Australia, similar to that of cutaneous melanoma.¹⁶ A caveat of our study was the high level of nonspecific coding topography for South Australia. Thus, cases from South Australia are likely marginally under reported and probably underrepresenting their incidence.

Although the 5-, 10-, and 15-year survival of CJM is high, no improvement from 1982 to 2015 years was observed, likely due to the lack of effective systemic therapeutics over this time. Remarkably, CJM tend to harbor similar mutations to that of cutaneous melanoma, with recurrent *BRAF* V600, *NRAS* Q61,^{25–27} *NF1*,²⁸ and *TERT* promotor^{15,26,27} mutations. Given that treatment of cutaneous melanoma greatly improved survival by targeting the MAPK pathway, molecular profiling of patients with CJM may also bring benefits and there is evidence that targeting this pathway has survival benefit in patients.²⁹ Furthermore, given that CJM appears

to have other similarities to cutaneous melanoma, including high levels of SNVs in SBS7 version 2 signature,¹⁴ it stands to reason that immunotherapies might be another suitable treatment option. Indeed, similar to MAPK inhibition, there is some promise with many studies noting patients with complete responses to therapy.²⁹ However, large-scale clinical trials are desperately needed, a difficult proposition given the rarity of the disease. Recently, a reasonably sized German study assessed the genetic characteristics of metastatic CJM and its relation to systemic treatment. Like other reported studies, the characteristic UV signature of C>T or CC>TT mutations were observed, with a moderate tumor mutational burden of 9 mutations/Mb,¹⁵ which appears to be similar to German cutaneous melanoma^{30,31} (although much lower than Australian populations³²), as well as approximately half of all patients harboring BRAF mutations. The authors found clear benefit from targeted BRAF inhibition or immunotherapy. However, even with the similarities to cutaneous melanoma, although the cohort is likely underpowered, the response to immunotherapy appears worse.^{15,33}

Additionally, given the low rate of metastases of previous CJM reports,^{34,35} it is unsurprising that death to other causes is more prevalent in the Australian population. Interestingly, after 12 years, men begin to have better relative survival compared to the population, increasing above the population level by 16 years post-diagnosis. This could likely be attributed to closer screening of lower risk patients and earlier detection and interventions of other diseases that would normally affect the male population. This effect is not observed in women, who by 30 years have a relative survival of 0.57. Last, unlike uveal melanoma,⁴ survival of CJM between states and territories is not significantly different. Unfortunately, a limitation of the Australian Cancer Database is the lack of disease-specific data that could be used for analysis (such as more refined topographical data). Furthermore, some data were encoded to nonspecific or unknown values which may cause over or underestimation of results. However, this effect would likely be minimal.

CONCLUSIONS

In conclusion, the incidence of CJM has increased in men, and significantly increased in women. Mortality has remained stable over the study period with minor differences between states and no difference in sexes.

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