

# Patient and Tumour Characteristics of Keratoacanthoma in a Large, Community-based Cohort Study from Queensland, Australia

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**Keratoacanthomas are common keratinocyte skin tumours. However, there is little community-based data published on the clinical features of keratoacanthoma. The aim of this study was to describe the patient and tumour characteristics of keratoacanthomas, as well as their treatment patterns. Data were obtained from the QSkin Sun and Health study, a prospective cohort of 40,438 randomly sampled and consented participants aged 40–69 years in Queensland, Australia. In 2010, a baseline survey collected data, including demography, phenotype, ultraviolet radiation exposure, medical history and lifestyle. Histopathological reports of keratoacanthomas arising until 30 June 2014 were reviewed. In total, 584 participants developed 738 keratoacanthomas; 18% of participants developed multiple tumours. Common patient characteristics were male sex (58%), age  $\geq 60$  years (76%), fair skin (80%), and previous history of actinic keratoses/keratinocyte cancers (89%). Keratoacanthomas were commonly located on the legs/feet (48%), and rarely on the the head/neck (7%). Excision was the most frequently used surgical method (71%) Evidence of histopathological regression was reported in 67% of keratoacanthomas, suggesting a potential for spontaneous resolution in a significant proportion of keratoacanthomas.**

*Key words:* keratoacanthoma/epidemiology; keratoacanthoma/aetiology; surveys and questionnaires; ultraviolet rays; dermatological surgical procedures.

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**K**eratoacanthoma (KA) is a common, but relatively understudied, tumour of the skin. KA are crateriform, squamoproliferative lesions defined by rapid proliferation over a period of 4–12 weeks (1–3), which sometimes undergo spontaneous regression (4). Although KA is generally considered a benign tumour, its morphology is similar to that of cutaneous squamous cell carcinoma (cSCC) (2). While some studies (5, 6) describe KA as having metastatic potential, the most

## SIGNIFICANCE

This study on the common skin tumour keratoacanthoma presents findings from a prospective cohort of 40,438 people from Queensland, Australia. Data on 584 people, who developed 738 keratoacanthomas, were collected from a self-reported survey and from pathology records. People with keratoacanthoma were more commonly men, aged  $\geq 60$  years, had fair skin, with a history of other skin cancers. Several participants developed multiple keratoacanthomas. In contrast to most previous studies, it was found that keratoacanthomas were commonly located on the legs/feet, and rarely located on the head/neck. Keratoacanthomas frequently showed histopathological signs of regression, suggesting that they may have potentially resolved spontaneously if left untreated.

widely accepted conclusion is that such uncommon metastatic tumours were cSCCs misdiagnosed as KAs, or sometimes represented a cSCC arising within a KA (4, 7–9). KAs may regress spontaneously, but the clinical resemblance to cSCCs and the consequent diagnostic uncertainty means that these tumours are routinely treated surgically. Histology remains the gold standard for diagnosis of KA.

There is a lack of literature on the aetiology of KA. Previous studies by us (10) and others (1, 2, 11–13) suggest that exposure to ultraviolet (UV) radiation plays a major role in development of KA. Other risk factors include male sex, older age, fair skin, smoking and high alcohol use (1–3, 10, 11). KA has been reported to be 10–20 mm in size and to most commonly develop on the head, neck and upper extremities (14–21).

There are very few population-based studies describing the clinical features of KA; most reports are single-institution studies featuring small numbers of patients (1, 3, 22). The current study used a large, prospective study to describe the features of a cohort of community-based patients with KA. This research extends a previous study (10), in which we investigated the risk factors for these tumours by focusing on the clinical and histological characteristics of the tumours, and documenting their treatment patterns.

## MATERIALS AND METHODS

### Study cohort and data collection

This study used data from the QSkin Sun and Health (QSkin) study (<https://www.qimrberghofer.edu.au/qskin2-research/>), which has been described in detail previously (23, 24). Between November 2010 and November 2011, 193,344 randomly sampled residents of the state of Queensland, Australia (population 4.6 million in 2010), aged between 40 and 69 years were invited by post to participate in the study. Participants received a baseline survey and 2 consent forms requesting permission for data linkage to cancer registries, pathology laboratories, public hospital databases and Medicare Australia (Australia's universal national health insurance scheme). Medicare records information on all medical services to Australian residents, except for those operated in public hospitals. A total of 43,794 people (19,920 men and 23,874 women) agreed to participate in the QSkin study, of whom 40,438 provided written consent for prospective data linkage. The data linkage approach enabled almost complete follow-up to be achieved for the consented participants. The responders were more likely to be women and in the older age-group (55–69 years).

Health administration data from Medicare Australia were used to identify participants treated for skin tumour excisions. From pathology laboratories across Queensland, all available histopathological reports were collected for skin tumour treatment until the end of June 2014; then details on all tumours with a clear histological diagnosis of KA were manually extracted. Equivocal tumours were not included: for example, non-specific squamoproliferative lesions. However, KAs with a cSCC arising from within the lesion were included, to ensure complete capture of all lesions identified by pathologists as KAs. Tumours that were classified as residual whenever there was an earlier report available for the initial surgical treatment were excluded. However, tumours classified as residual/recurrent if no initial report existed were included. The tumours were not re-reviewed by a pathologist. From the histopathological reports, information was collected on: anatomical location; tumour size; co-occurrence with other pathologies in the same histological specimen; sun damage in the surrounding skin; stage of tumour development; perineural invasion; provider type; surgical method; and complete excision. Tumour size was defined as the largest diameter, measured horizontally on the skin surface, as noted in the macroscopical measurement in the histopathological report. Importantly, the tumour is subject to slight shrinkage after excision and formalin fixation (25), and thus clinical and histopathological measurements may not correspond exactly. Co-occurrent diagnoses in the same specimen were subdivided as: low-grade squamous cell dysplasia (including actinic keratosis), high-grade squamous cell dysplasia (including intraepidermal carcinoma), squamous cell carcinoma; and others (benign lesions including seborrheic keratosis, verruciform epidermal hyperplasia, benign naevi, lichen simplex chronicus and solar lentigo).

In the histopathological reports, words such as “active growth”, “early”, and “proliferative” were taken to represent histological proliferation, whereas “abortive”, “regressing”, and “lichenoid/lymphocytic regression” were inferred as histological regression. If the pathologist expressed that the margins were clear, even with narrow margins, this was regarded as a complete excision. A validation of the manual report review was performed, using a 10% sample of the KAs, finding negligible differences between the 2 independent reviewers. From the baseline survey, self-reported data were collected on demographics, phenotypic characteristics, medical history, lifestyle and information about previous treatment of skin cancer and other skin lesions.

Approval for this study was obtained from QIMR Berghofer Medical Research Institute Human Research Ethics Committee in Brisbane, Australia, and all study participants provided consent to take part.

### Statistical analysis

A descriptive analysis of individuals with incident KA and their tumour characteristics was performed. Medians, range and inter-quartile range (IQR) were calculated for continuous variables, and frequency distributions for categorical variables, to investigate the differences in distribution of characteristics. Pearson  $\chi^2$  statistics were used to test the statistical significance of the differences in the distribution for categorical variables. For the variable relating to tumour size, the differences between the sexes, between age

**Table I. Frequency distribution of patient characteristics for keratoacanthoma (KA) in the QSkin study**

Characteristics	Participants with KA (n = 584) n (% <sup>a</sup> )
Age at diagnosis	
< 50 years	34 (5)
50–< 60 years	147 (20)
≥ 60 years	557 (75)
Missing	0
Sex	
Female	245 (42)
Male	339 (58)
Missing	0
Skin colour	
Fair	466 (80)
Medium	108 (19)
Olive/dark	8 (1)
Missing	2
Sunburn tendency	
Not burn	30 (5)
Burn a little	189 (33)
Burn moderately	221 (38)
Burn badly	140 (24)
Missing	4
Tanning ability	
Not tan	93 (16)
Tan a little	172 (30)
Tan moderately	244 (42)
Tan deeply	70 (12)
Missing	5
Freckles on the face at age 21 years	
None	216 (37)
A few	161 (28)
Some	129 (22)
Many	75 (13)
Missing	3
Previous skin cancers removed surgically	
None	96 (17)
1	61 (11)
2–10	263 (46)
11–20	83 (14)
> 20	75 (13)
Missing	6
Previous actinic keratoses/skin cancers frozen or burnt off	
None	64 (11)
1–5	109 (19)
6–10	58 (10)
11–20	93 (16)
21–50	92 (16)
> 50	164 (28)
Missing	4
Smoking status	
Never smoker	277 (48)
Past smoker	214 (37)
Current smoker	90 (15)
Missing	3
Multiplicity of KA tumours among participants	
1 tumour	481 (82)
2 tumours	71 (12)
> 3 tumours	32 (6)
Missing	0

<sup>a</sup>Due to rounding, percentages may not add up to 100%.

**Table II. Frequency distribution of tumour characteristics for keratoacanthoma (KA) in the QSkin study**

Characteristics	KA tumours (n = 738) n (% <sup>a</sup> )
<b>Anatomical location</b>	
Head and neck	53 (7)
Arms and hands	238 (33)
Trunk	89 (12)
Legs and feet	352 (48)
Missing	6
<b>Tumour size (mm)<sup>b</sup></b>	
1–5	67 (13)
6–10	279 (53)
11–15	151 (28)
16–20	27 (5)
>20	7 (1)
Missing <sup>c</sup>	207
<b>Co-occurrence with other pathologies in the same specimen</b>	
KA only (i.e. co-occurrence not stated <sup>d</sup> )	666 (90)
Low-grade squamous cell dysplasia (e.g. actinic keratosis)	21 (3)
High-grade squamous cell dysplasia (e.g. intraepidermal carcinoma)	7 (1)
Squamous cell carcinoma	13 (2)
Others (benign lesions)	31 (4)
<b>Sun damage in surrounding skin</b>	
No	1 (0.1)
Yes	41 (6)
Not stated	696 (94)
<b>Stage of tumour development</b>	
Proliferative	114 (33)
Regressive	230 (67)
Not stated	394
<b>Perineural invasion</b>	
Yes	2 (0.3)
Not stated <sup>d</sup>	736 (99.7)

<sup>a</sup>Due to rounding, percentages may not add to 100%. <sup>b</sup>Tumour size was defined as the largest diameter (in mm) measured horizontally in the skin surface, as noted in the macroscopic measurements in the histopathological report. <sup>c</sup>For the item "tumour size", "not stated" included tumours where the tumour size was not stated in the histopathological report, as well as incompletely excised tumours. <sup>d</sup>For the items "co-occurrence" and "perineural invasion", it was assumed for the analysis that "not stated" equated to "not present".

**Table III. Frequency distribution of treatment patterns for keratoacanthoma (KA) in the QSkin study**

Treatment patterns	KA tumours (n = 738) n (% <sup>a</sup> )
<b>Provider type</b>	
Primary care physician	604 (82)
Dermatologist	81 (11)
Plastic surgeon	15 (2)
General surgeon	10 (1)
Other medical specialists	28 (4)
Missing	0
<b>Surgical method</b>	
Excision	523 (71)
Punch biopsy	50 (7)
Shave biopsy	90 (12)
Curettage	71 (10)
Missing	4

<sup>a</sup>Owing to rounding, percentages may not add to 100%.

groups, and between anatomical locations were analysed using the Kruskal–Wallis test. Missing data for the patient and tumour characteristics are reported in **Tables I–III**.

All data were analysed using SAS 9.4 (SAS Institute Inc., SAS Campus Dr. Cary, NC, USA).

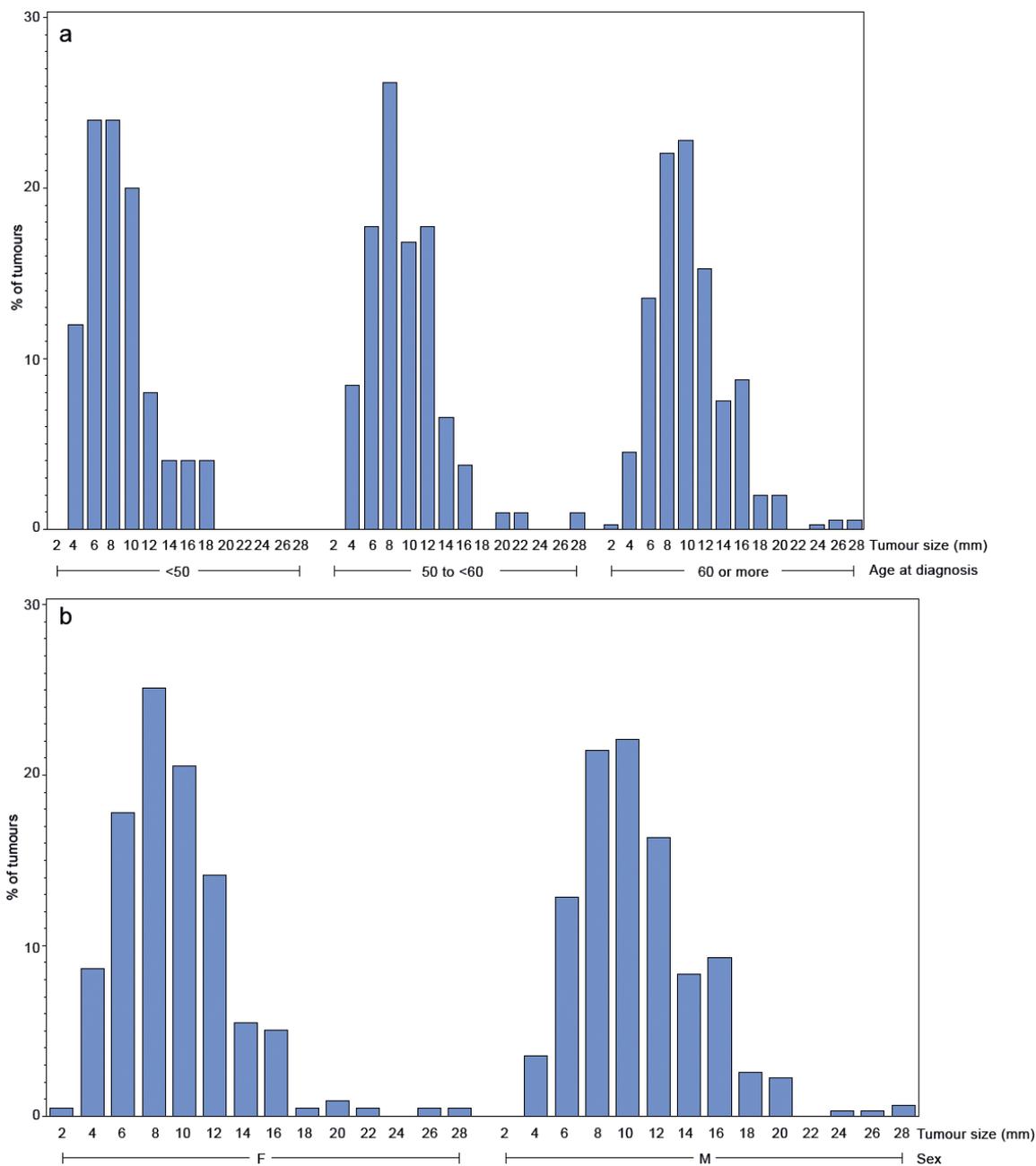
## RESULTS

### Patient characteristics

During a median follow-up period of 3.0 years, 584 (1%) participants developed 738 KAs, with a median age at diagnosis of 64 years (IQR 59–68). A majority of the participants with KA were men (58%) (Table I), despite the fact that, overall in the QSkin cohort, there were fewer men (46%) than women (23). Participants with KA most commonly had fair skin (80%) with a moderate tendency to sunburn (38%), and to tan (42%), and 63% had at least a few freckles on the face at age 21 years (Table I); these are phenotypic features, which we have also described in our earlier publication (10) on risk factors of KA. In this high-incidence Queensland population, 83% of the participants with KA reported having had at least one skin cancer surgically excised and 89% reported at baseline having had at least one skin cancer/actinic keratosis treated destructively. Most patients had only one histologically confirmed KA during follow-up, but 18% developed multiple tumours, and the number of confirmed KA lesions per patient ranged up to 13. Tumour multiplicity was slightly more frequent among participants aged  $\geq 60$  years (20%), compared with those aged 50 to  $< 60$  years (13%) and  $< 50$  years (14%), although not reaching statistical significance. There was no significant difference in tumour multiplicity across the sexes. Among patients with KA, 15% were current smokers and 37% were past smokers (Table I).

### Tumour characteristics

The majority of the KAs among QSkin participants were located on the legs and feet (48%) and arms and hands (33%, and, more rarely, on the trunk (12%) and head and neck (7%) (Table II). The anatomical distribution of tumours was similar for men and women. The median tumour size for all participants was 9 mm (range 2–28 mm). People aged  $\geq 60$  years were diagnosed with larger tumours (10 mm, IQR 7–12) compared with those aged 50 to  $< 60$  years (8 mm, IQR 6–11) and  $< 50$  years (7 mm, IQR 6–10);  $p = 0.004$  (Fig. 1a). Furthermore, men were diagnosed with larger tumours (10 mm, IQR 7–12) than women (8 mm, IQR 6–11);  $p < 0.001$  (Fig. 1b). The largest KAs developed on the legs and feet (10 mm, IQR 8–12), followed by KAs on the arms and hands (9 mm, IQR 7–12), trunk (8 mm, IQR 6–10) and head and neck (6.5 mm, IQR 5–11);  $p < 0.001$ . Most of the KAs (90%) did not occur contiguously with any other lesion



**Fig. 1. Tumour size by:** (a) age at diagnosis; and (b) sex. M: male; F: female.

type, although co-occurrence with other pathologies in the same histological specimen did occur: most commonly for benign seborrhoeic keratosis (4%), followed by low-grade squamous cell dysplasia (3%), squamous cell carcinoma (2%) and high-grade squamous cell dysplasia (1%) (Table II). In 6% of tumours, sun damage in surrounding skin was reported. Two-thirds (67%) of the tumours removed were in a histopathological stage of regression, however in more than half (53%) of the reports the stage was not stated. Only 0.3% ( $n=2$ ) histopathological reports noted the presence of perineural invasion (Table II).

*Treatment patterns*

The majority of KAs were treated by primary care physicians (82%), followed by dermatologists (11%) (Table III). The most commonly used surgical method was excision (71%), as opposed to punch biopsy (7%), shave biopsy (12%) and curettage (10%). Of the KAs treated with excision, almost all (97%) had clear margins. Primary care physicians preferred surgical excision (76%) over other treatment methods, as did general surgeons; plastic surgeons; and other medical specialists when combined (81% surgical excisions). Conversely,

dermatologists chose excision in a smaller proportion of the lesions (32%) ( $p < 0.001$ ). Instead, dermatologists chose other methods: shave biopsy (28%) and curettage (41%).

## DISCUSSION

This large community-based prospective cohort study from Queensland, Australia, described the clinical and histological characteristics of incident (newly arising) KAs. People with KA were most likely to be male, aged 60 years or more, have fair skin, and report a previous history of actinic keratoses or keratinocyte cancers. Tumour multiplicity was common. In contrast to most of the previous literature, this study found that KAs are commonly located on the legs and feet, and that tumours on the head and neck were much less frequent. For the first time in a large community-based study, this study also reports treatment patterns of KA; excision was the most frequently used surgical method, and a majority of KAs showed histological signs of regression.

There were more men than women with KA, despite the study sample having more women overall. This corresponds with earlier research showing that men develop more KAs than do women (17, 20, 26). Similar to the current study, previous reports have shown that the incidence of KA increases with age (15, 17, 20, 27). Participants with KA commonly had a sun-sensitive phenotype and a past history of actinic keratoses and other keratinocyte cancers, which supports aetiological theories of high cumulative sun exposure on a background of phenotypic susceptibility (probably genetic) (17, 20, 28–30). Participants frequently developed multiple tumours in the current study (18%), as well as in previous studies of KA (8%) (15, 19). This is also similar to findings for other keratinocyte cancers, where tumour multiplicity is common (31). The ratio of KA to cSCC within the cohort was 1:3 (10), indicating that KA is a very common tumour in Queensland.

This study observed a median tumour diameter of 9 mm, which is slightly smaller than the 13 mm described in a study of KA (32) that used clinical measurements as opposed to histopathological measurements, even when considering the shrinkage effect of 16–18% (2.1–2.3 mm) that was reported in a previous study (25). The smaller size measured in the current study could reflect early clinical presentation as a consequence of heightened awareness of skin cancer in the Queensland population, coupled with the proclivity of practitioners towards early detection and treatment of skin pathology. Notably, men were diagnosed with larger KAs than women, similar to previous reports on larger tumours and delayed care-seeking among men with cSCC (33, 34).

The current community-based study found that KAs occurred far more frequently and were slightly larger on the legs and feet than on the head and neck areas.

This differs from most earlier reports (14–21), including a single-centre study from Pittsburgh, USA, where the most common site for KA was the head and neck area (69%) followed by the upper extremities (14, 21). A population-based study in Hawaii, USA, reported tumours to be located on the upper extremities (56%), followed by the head and neck, and trunk (17). An earlier multicentre study from Queensland, Australia ( $n = 655$ ) reported similar proportions of KAs arising on the head and neck area (25%), upper extremities (26%), and lower extremities (27%) (20). A study from 2 centres in Houston and Minnesota, USA, reported the face and the upper extremities to be common locations for KA in men, whereas women developed more lesions on the lower extremities (15). Only 1 previous study showed similar anatomical distributions to the current findings; a single-centre study from California, USA ( $n = 399$ ) where most tumours presented on the lower extremities (40%), followed by upper extremities (36%), head and neck (16%) and the trunk (9%) (16). There are several possible reasons for the differences between the present series and earlier reports. Firstly, the present study is community-based, with cases identified prospectively within a cohort sampled randomly from the general population of a large jurisdiction. To our knowledge, most previous studies were from dermatology departments or hospitals. This may have caused a skewed distribution, with a higher proportion of head and neck tumours being referred to specialist surgery at a dermatology clinic or hospital. In addition, most of the earlier literature is decades old, and probably reflects quite different patterns of ultraviolet radiation exposure and sun-protection habits in earlier birth cohorts.

A few previous studies have described atypical cases of KAs showing signs of perineural invasion (21, 32, 35, 36). In a recent systematic review by Savage et al., as many as 10% of the tumours showed evidence of perineural invasion (4), while other studies have reported lower proportions, of 1–4% (32, 35). In contrast, the current study found perineural invasion to be very rare in KA (0.3%), although we cannot exclude the possibility that pathologists may have omitted to report on invasion of nerve structures. We consider this an unlikely explanation; it is more likely that earlier studies were limited by referral bias, whereby more challenging cases have been referred to specialized centres with an interest in KA pathology. Previous literature does not implicate that perineural invasion affects the prognosis, although the studies included a very small number of participants (21, 32, 35).

It is notable that most KAs in the current study were removed in a stage of histological regression. To our knowledge there are no previous reports describing the histological stage of development of KA. The high proportion of regressing tumours could indicate that spontaneous resolution of KA is very common. In a

systematic review by Savage et al. (4), 52/445 cases regressed clinically without treatment. This finding supports the theory that spontaneous resolution is a common characteristic of KAs.

The vast majority of KAs in the current study were treated by primary care physicians, as is commonly the case for other skin tumours in Australia (37). The gold standard for KA diagnosis today is histopathology, and to achieve this, surgery or a biopsy is necessary. The choice of surgical method is commonly influenced by factors such as anatomical location and tumour size, aesthetic considerations and type of practitioner. To our knowledge there are no previous studies reporting the frequency distribution of surgical treatment methods for KA. In the current study, excision was by far the most common surgical method (71%), followed by shave biopsy, curettage, and punch biopsy as the least common method.

#### *Strengths and limitations*

The strengths of this study include the large size and the prospective, community-based study design with a comprehensive baseline survey and close to complete follow-up data. A major benefit was the access to histopathological reports, as opposed to self-reported tumours. In addition, the universal healthcare system of Australia (Medicare) enabled the collection of information on all medical services provided to Australian residents (23). The high incidence of skin cancer in Queensland (23, 38) ensured that a large number of cases would arise in relatively short duration, especially when compared with other studies. Furthermore, the repeatability of the manual review of histopathological reports was tested, and showed very high congruence between the 2 independent reviewers.

Limitations of this study include the use of self-reported survey items, which can introduce misclassification of exposure, although systematic recall bias is not possible since information was collected at baseline. In addition, good repeatability of the QSkin survey items has been shown in a previous publication (24). It is possible that some of the KAs in the current study were misdiagnosed cSCCs (for example, the follicular infundibular variant) (39); and, conversely, KAs misdiagnosed as cSCCs may have been excluded from the current study. Variables were extracted from histopathological reports using standardized criteria for the tumour characteristics, as opposed to re-reviewing tumours. This could result in missing data for some tumour characteristics (e.g. for the variables tumour size, sun-damage in surrounding skin and stage of tumour development). Although it is likely that the pathologist would have noted these variables, if present, we cannot be certain. Indeed, this study highlights the problem of non-standard reporting. We advocate that dermatology and pathology societies should standardize the reporting of KAs, so that clinicians

and patients have access to complete information on the characteristics of the tumours. Another limitation concerns our reporting of the stage of tumour development; we cannot be sure that signs of histopathological regression results in spontaneous resolution of the KA. First, the KAs in the current study all underwent surgery, meaning that the natural history of these tumours is unknown. In addition, histopathological regression may be present only in some smaller areas of the tumour. Furthermore, regression is one of the diagnostic clues for KA, but not all KAs resolve spontaneously.

#### *Conclusion*

This large, community-based study provides a broad overview of the patient and tumour characteristics of KA and their treatment patterns in a high-incidence population. Patients with KA were most likely to be male, aged 60 years or more, and to have a sun-sensitive phenotype. Tumour multiplicity was common. In this cohort, KAs were most likely to arise on the lower limbs and less likely to arise on the head and neck. Importantly, this study found a high proportion of histologically regressing tumours, indicating that spontaneous resolution of KA may be common. Much remains to be learned about these intriguing tumours; future research will explore their genetic, molecular and immunological characteristics.

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