Oral Oncology 98 (2019) 109–117

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Cutaneous keratinocyte cancers of the head and neck: Epidemiology, risk factors and clinical, dermoscopic and reflectance confocal microscopic features

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ARTICLE INFO

Keywords:
Basal cell carcinoma
Squamous cell carcinoma
Actinic keratosis
Keratoacanthoma
UV exposure
Dermoscopy
Reflectance confocal microscopy
Environmental risk factors
Genetic risk factors

ABSTRACT

Keratinocyte cancers are the most common malignancy among people with European ancestry, and are very common on sun-exposed areas of the head and neck. Incidence is directly correlated with latitude and annual ultraviolet radiation incidence, although there are a number of other environmental, occupational and genetic risk factors, and keratinocyte cancers become more common at middle age. Basal cell carcinomas (BCC) are the most common, comprising 80% of keratinocyte cancers, but have a very low rate of metastases and low mortality. Squamous cell carcinomas (SCC) make up 20% of keratinocyte cancers, and have relatively infrequent metastases, at 5–16%. While there are no precursor lesions for BCC, SCC represents the final stage in a spectrum of cellular atypia and dysplasia, from actinic keratoses to in situ SCC to invasive SCC. Dermoscopy is a well-established diagnostic tool for keratinocyte cancers, and reflectance confocal microscopy is emerging as another useful diagnostic tool, particularly on functionally and cosmetically sensitive sites like the face.

Introduction

Keratinocyte cancers, also called non-melanoma skin cancers, occur in people of all skin types but most often in fair-skinned people, and are the most common malignancy among European-background people. In fair-skinned people, 25% of keratinocyte cancers are squamous cell carcinoma (SCC) and 75% are basal cell carcinoma (BCC), although recent studies suggest that SCCs are becoming proportionately more common, and incidence of both types is rising worldwide [1,2].

Keratinocyte cancer incidence is directly correlated with latitude and average annual ultraviolet radiation (UV) incidence, with locations closer to the equator and receiving higher levels of UV having higher rates of keratinocyte cancers. Incidence also increases with age, in line with cumulative UV exposure as a risk factor. Keratinocyte cancers are more common in women when they appear before 40 years of age, but become more common in men as age increases, and by age 80 the ratio of male to female patients is 2–3:1. In the high UV environment of Australia, the cumulative risk to age 70 of having a keratinocyte cancer is 58% for women and 70% for men [1].

Basal cell carcinoma

BCC is the most common skin cancer in humans, and is very common on the face, particularly the nose. In recent decades incidence rates have risen steeply, between 20% and 80%. Men are more likely than women to develop BCC, at a ratio of 1.5–2:1, and the median age of onset is 68 years [1]. It arises only on skin with pilosebaceous units, but there is some debate about the exact site and origin cells. While various studies have suggested that BCC may arise from stem cells within hair follicles, recent work suggests that the interfollicular epidermis is also a likely location [3]. Patients typically present with a non-healing, steadily enlarging lesion that may also be itchy or bleeding [2].

BCCs typically do not metastasise, but rather have a pattern of locally invasive growth and tissue destruction, causing significant morbidity [2,4]. BCCs have increased production of enzymes such as collagenases, which degrade the surrounding tissue and facilitate tumour expansion. However, BCCs appear to be dependent on a specific stroma produced by dermal fibroblasts; when transplanted away from this particular stroma, they differentiate into benign keratin-filled cysts [4]. Because of this low rate of metastases, mortality from BCC is rare and

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https://doi.org/10.1016/j.oraloncology.2019.09.019
Received 31 May 2019; Accepted 18 September 2019
Available online 01 October 2019
1368-8375/

occurs mainly in immunocompromised patients and patients with basal cell nevus syndrome. Age-adjusted mortality is estimated to be 0.12 per 100 000 [1]. Where metastasis does occur, it is most common on the mid-face region and around the ears, including the nasal dorsum, tip and ala, nasolabial folds, philtrum, inner canthus, forehead, auricular and periauricular areas [5].

At least 26 histopathologic subtypes of BCC have been described, but there is no universally-accepted classification scheme. In addition, many lesions have elements of more than one clinicopathologic pattern. However, BCCs can generally be assigned to one of five major clinicopathologic types: nodular, superficial, infundibulocystic, morpheaform and fibroepithelial. Micronodular and basosquamous are two important histopathological types [6]. Among all types of BCCs, ulceration is a common feature. BCCs are typically amelanotic, but can also be pigmented or partially pigmented, mostly in people with darker skin [1,2].

Nodular BCC is the most common type, accounting for 50% to 80% of all BCCs, and is particularly prevalent on the face; approximately 90% are found on the head and neck. These lesions begin as shiny or pearly papules or nodules, often with branched vessels (arborizing telangiectasias) visible either clinically or with dermoscopy. The surface is usually smooth but as the lesion enlarges, it can ulcerate in the centre, surrounded by a rolled, elevated border. Micronodular BCCs are a histopathological subtype that appears in 15% of all BCCs, featuring smaller aggregations of basaloid cells infiltrating the dermis with no apparent connection to the epidermis. They can be difficult to differentiate clinically from nodular or superficial BCCs. These lesions are more likely to recur, due to multi-focal and subclinical spread beyond the borders of clinically visible papules or plaques [1,2,5].

Superficial BCCs, accounting for 10% to 30% of BCCs, are well-circumscribed erythematous patches or macules, or thin plaques or papules. They commonly have focal patches of scale or crusts, variable amounts of pigmentation, and a thin, rolled border. Growth of superficial BCCs is mainly horizontal, but as they enlarge they can develop induration, ulceration, or a more nodular shape if they become invasive. They range between a few millimetres and a few centimetres in diameter, and are more common on non-facial sites. This form of BCCs frequently recurs after routine treatment by excision, due to subclinical lateral spread beyond the borders of the obvious lesion [1,2].

Infudibulocystic BCCs are rare but usually arise on the head and neck of older patients, as well-circumscribed pearly papules. They can be mistaken for benign follicular adnexal abnormalities, and show follicular differentiation on histopathology [2].

Morpheaform BCCs, also called morphea-like, fibrosing, sclerosing, or syringomatous BCC, comprise less than 10% of BCCs and are also commonly found on the head and neck. They are slightly elevated or slightly depressed, smooth, pink or white patches with poorly-defined borders, often resembling a scar or plaque of morphea. Telangiectasia, crusts and ulceration are sometimes present. This form is relatively aggressive and can cause extensive destruction of local tissue [1,2].

Fibroepithelial BCCs, also called fibroepithelioma of Pinkus, is a sessile plaque or pedunculated papulonodule, usually pink or skin-coloured with a smooth surface. These BCCs are more common on the lower back than the head and neck [1].

In addition to these main clinico-pathologic types, basosquamous carcinoma appears histopathologically to have features of both BCC and SCC. While relatively rare, at 1% of all keratinocyte cancers, this form is more aggressive than most BCC types and approximately 5% will metastasise. These lesions appear most commonly on the head and neck [1,2].

Squamous cell carcinoma

Incidence of SCC has been rising worldwide for several decades. SCCs become more common with advancing age, with incidence increasing steeply after 60 years of age, and is more common in men than women [1]. SCCs on highly sun-damaged skin have relatively infrequent metastases, at less than 5%. Thicker SCCs are more likely to metastasise but even in tumours > 6 mm thick, only about 16% metastasise. However, SCC location on the lip or ear is another risk factor for metastasis, and SCC on the central zone of the face, temples, lips, ears and scalp are more likely to recur [4,5]. Mortality from SCC in the general population is low, although higher than mortality for BCCs, but in patients over 85 years of age the majority of skin cancer deaths are caused by SCC, and SCC is a significant cause of mortality in organ transplant patients. Age-adjusted mortality is estimated at 0.26 per 100, 000 [1]. Unlike BCC, SCC develops along a spectrum of cellular atypia or dysplasia, from precursor lesions to SCC in situ to invasive SCC.

Precursor lesions: Actinic keratosis

Actinic keratoses (AKs) are SCC precursor lesions with squamous cell dysplasia limited to the epidermis and solar elastosis, and are very common on chronically sun-exposed skin in middle-aged and older European-background individuals. They are one of the most common lesions seen in clinical practice and it has been estimated that up to 12% of all people in the US have AKs [1]. While they are recognised as SCC precursor lesions, the risk of each individual AK progressing to an invasive SCC is 0.075%-0.096% per year, and they may spontaneously regress [1,4].

AK lesions range in size from a few millimetres to large patches several centimetres across. Early AKs are typically a rough erythematous plaque with white or yellow scale, while more advanced AKs are thicker, with well-defined borders and obvious erythema and hyperkeratosis. However, several variants are more difficult to diagnose. Some lesions present as light scale with indistinct borders and no erythema; others become hyperkeratotic or develop a cutaneous horn, making them difficult to distinguish clinically from SCCs. Pigmented AKs, which may develop a reticulated appearance, often lack erythema and can be difficult to distinguish clinically from seborrheic keratosis, a solar lentigo or even a lentigo maligna (melanoma in situ on severely photodamaged skin), and tend to appear on the face. Lichenoid AKs are similar to typical AKs, but with a dense band of infiltrate that gives them more erythema and may cause itchiness or tenderness. Atrophic AKs are pink to red macules, rather than plaques, with light scale [1,4].

An important clue in all these cases is the presence of photodamage around the lesion, such as telangiectasia, solar elastosis and irregular pigmentation. Visual inspection should also be combined with palpation to detect a keratotic base or tenderness, especially on skin that is chronically erythematous from photodamage [1,4].

AKs typically cluster on the most chronically sun-exposed sections of skin, and so are very common on the head and neck, especially the upper forehead, any bald scalp, upper helices of the ears, supraorbital ridge, bridge of the nose, and malar eminences [1,4].

SCC in situ (intraepidermal carcinoma or Bowen disease)

Bowen disease or intraepidermal carcinoma are common names for SCC in situ, most commonly presenting as a pink, scaly plaque or patch on sun-damaged skin on the head or neck. Verrucous forms may clinically resemble warts or seborrheic keratoses. Pigmented SCC in situ sometimes occurs, and can be mistaken for a pigmented AK or a melanoma [1].

Invasive SCC

Invasive SCCs can be papulonodular, plaque-like, papillomatous or exophytic. Generally, they are skin-coloured or pink to red, and occasionally pigmented; scale is often present and some lesions become very hyperkeratotic. Crusting, erosions and ulcerations also appear, and some lesions become tender or painful; pain, paraesthesia or anaesthesia can indicate perineural invasion. Invasive SCC can grow slowly

or rapidly [1].

Invasive SCC is staged by lesion diameter and depth of invasion. Lesions on the ear or the lips are more likely to show aggressive characteristics on histopathological examination, compared to other sites on the head and neck [1]. SCCs may also be poorly-, moderately- or well-differentiated, with poor differentiation an independent risk factor for recurrence and metastasis. Highly differentiated tumours often have a broad, rounded margin that extends into the dermis, and often feature keratinization. Some tumours feature papillomatous extensions and cord-like extensions of mildly dysplastic squamous epithelia reaching into the epidermis. More poorly-differentiated tumours can display anaplastic cytology, and require immunohistochemical staining to confirm them as SCCs [4].

Keratoacanthoma

While there is some debate as to whether keratoacanthomas (KA) are true SCCs or a benign pseudomalignancy, they do have a number of characteristics that separate them from classical invasive SCCs. KAs are typically rapidly growing papules that become crateriform nodules with a keratotic core. Most are solitary tumours 5–15 mm in diameter, but can become several centimetres in diameter. Unlike classical SCCs, they often resolve over several months to leave an atrophic scar. Like classical SCCs, they form mainly on the head and neck or sun-exposed extremities, but have also been associated with immunosuppression, BRAF inhibitors, HPV infection and chemical exposures [1].

Environmental and occupational risk factors

UV exposure is the major environmental risk factor for both BCCs and SCCs, particularly in skin phototypes I and II. One study found that 75.7% of coding mutations in BCCs had a UV signature. For BCC, intermittent, intense UV exposure, often in a recreational setting, and sunburns at any age seems to be a stronger risk factor than lifetime cumulative exposure. In contrast, for SCC, high cumulative levels of UV exposure and sunburns during childhood are the major risk factor [1,2]. UV exposure can also lead to field cancerization, areas where keratinocytes have UV-specific precancerous genetic mutations and which have a much higher risk of SCC development than other parts of the skin on the same patient [7].

Indoor tanning is also an independent risk factor for keratinocyte cancer development, with an odds ratio of 1.5 for BCC and 2.5 for SCC even after adjusting for other UV exposures. Even therapeutic UVR exposure slightly increases BCC and SCC risk in a dose-dependent manner, if the therapy is prolonged [1,2].

Ionizing radiation, including medically-administered ionizing radiation, is another risk factor for keratinocyte cancers, with risk rising in proportion to the dose, generally a threefold increased risk. In particular, children who were treated with ionizing radiation for tinea capitis are at a 3.6-fold risk of multiple BCCs on the head and neck in adulthood. Pilots, who are exposed occupationally to increased levels of ionizing radiation at flight altitude, have an increased risk of BCC and SCC. There is a long latency period between any ionizing radiation exposure and keratinocyte cancers arising, usually 20 years or more [1].

In addition, chronic injury or irritation, including from infrared radiation, is a risk factor for SCC. The site of thermal burns or chronic ulcers are more likely to develop SCCs. Personal heaters using an ignited coal in a container that is held under the clothes, such as the Kangri in Kashmir, or coal-heated bed platforms, such as the kang in China, cause repeated exposures to moderate heat sources that can cause erythema ab igne and eventually progress to SCC [1,8].

Several organic chemicals, particularly with occupational exposure, are linked with an increased risk of SCC, particularly multiple SCCs located on one body part; however, these are more common on the arms and rarer on the head and neck. These chemicals include asphalt, tar, arsenic, pesticides and polycyclic aromatic hydrocarbons. As with ionizing radiation, there is a long latency period, with tumour development typically occurring 20–40 years after exposure. Extensive arsenic exposure has also been associated with an increased BCC risk. Pilots, sailors, agricultural workers, locomotive engine drivers, and textile workers are at an increased risk of BCC and SCC due to occupational exposures to these risk factors. Several of these occupations combine high UV exposure and potential chemical risk factor exposure [1].

Immunosuppression subsequent to organ transplantation is a strong risk factor for development of keratinocyte cancers, with BCC risk in organ transplant recipients 4.1 to 6.9-fold higher and SCC risk 15 to 357-fold higher than in the general population. In addition, keratinocyte cancer risk increases with time after transplantation, with cumulative BCC incidence in Australian transplant recipients rising from 21.5% in the first 5 years to 64.3% after 20 years, and SCC incidence rising from 16.9% to 75% for the same time period. Transplant recipients are also more likely to develop metastases or local recurrences of SCCs, and SCC is a significant contributor to morbidity and mortality in transplant recipients [1,9]. Use of systemic immunomodulatory drugs, including new biologic drugs, also increases BCC and SCC risk. In particular, up to 25% of patients treated with BRAF inhibitors develop SCCs or keratoacanthomas. Lesions begin appearing within weeks of starting BRAF inhibitor treatment, usually on patients who already have photodamaged skin. However, combined BRAF and MEK inhibitor treatment does not have an increased risk of SCC [1].

Human papillomaviruses (HPV) are thought to act as a co-carcinogen with UV exposure and has been implicated in early SCC development on sun-exposed sites. Patients with HIV are also at an increased risk of HPV-associated SCCs [1].

Genetic risk factors

Genome-wide association studies and candidate gene studies suggest approximately 30 susceptibility loci for BCC development and at least 11 susceptibility loci for SCC development [1], including pigmentation loci that cause light skin, hair and eye colour, freckling, and poor tanning ability (Table 1). Many of the identified genes have small effect sizes, with OR of 1.15 to 1.5, so are of limited utility in risk prediction on their own. However, due to the large number of susceptibility loci, polygenic risk scores may become feasible in the future to identify and target patients who would benefit from extra screening or earlier intervention [10].

Several genetic syndromes are also associated with an increased risk of keratinocyte cancers. Basal cell naevus syndrome, caused by an inactivating mutation in *PTCH1* or *PTCH2*, predisposes patients to multiple early-onset BCCs, along with other neoplasms such as fibromas and medulloblastoma, skeletal anomalies, and cutaneous anomalies such as palmoplantar pits. Bazex-Dupré-Christol syndrome, a rare, usually dominant X-linked condition, features multiple, usually facial BCCs developing during the second decade of life, along with other hair follicle anomalies. The similar Rombo syndrome also features BCCs [1].

Xeroderma pigmentosum, featuring serious defects in DNA repair, predisposes patients to UV-driven skin cancers, with a 4800-fold increased risk of paediatric-onset multiple skin cancers. Similarly, oculocutaneous albinism syndromes, where lack of pigment predisposes patients to higher levels of UV damage in the skin, increases the risk of UV-driven BCCs and SCCs [1].

Epidermodysplasia verruciformis, a condition where there is widespread skin colonisation with HPV, is associated with SCCs appearing several decades earlier than usual onset and usually on sun-exposed skin, in line with HPV's proposed role as a co-carcinogen with UV radiation. Dystrophic epidermolysis bullosa, caused by mutations in type VII collagen and leading to significant scarring, features early-onset, multiple, unusually aggressive SCCs, which are the most common cause of death in these patients [1].

Table 1
Genetic susceptibility loci for keratinocyte cancers.

Gene	Locus/rs number	Condition	BCC	SCC	References
XPA	9q34	Xeroderma pigmentosum	+	+	[2,7]
XPB	2q21	Xeroderma pigmentosum	+	+	[2,7]
XPC	3p25.1	Xeroderma pigmentosum	+	+	[2,7]
XPD	19q13.2	Xeroderma pigmentosum	+	+	[2,7]
XPE	11	Xeroderma pigmentosum	+	+	[2,7]
XPF	16p13.3	Xeroderma pigmentosum	+	+	[2,7]
XPG	13q32-33	Xeroderma pigmentosum	+	+	[2,7]
XPV	6p21.1	Xeroderma pigmentosum	+	+	[2,7]
TGFBR1	9q22.3	Ferguson-Smith syndrome		+	[7]
TYR	11q14.3	Oculocutaneous albinism		+	[7]
OCA2	15q12-13	Oculocutaneous albinism		+	[7]
TYRP1	9p23	Oculocutaneous albinism		+	[7]
SLC45A2	5p13.2	Oculocutaneous albinism		+	[7]
SLC24A5	15q21.1	Oculocutaneous albinism		+	[7]
C10Orf11	10q22.2–22.3	Oculocutaneous albinism		+	[7]
EVER1	17q25.3	Epidermodysplasia verruciformis		+	[7]
EVER2	17q25.3	Epidermodysplasia verruciformis		+	[7]
COL7A1	3p21.3	Epidermolysis bullosa (dystrophic)		+	[7]
LAMA3	18q11.2	Epidermolysis bullosa (junctional)		+	[7]
LAMB3	1q32	Epidermolysis bullosa (junctional)		+	[7]
LAMC2	1q25-31	Epidermolysis bullosa (junctional)		+	[7]
COL17A1	10q24.3	Epidermolysis bullosa (junctional)		+	[7]
FANCA	16q24.3	Fanconi anaemia		+	[7]
FANCB	Xp22.31	Fanconi anaemia		+	[7]
FANCC	9q22.3	Fanconi anaemia		+	[7]
FANCD1/BRCA2	13q12.3	Fanconi anaemia		+	[7]
FANCD2	3p25.3	Fanconi anaemia		+	[7]
FANCE	6p21.3	Fanconi anaemia		+	[7]
FANCF	11p15	Fanconi anaemia		+	[7]
FANCG/XRCC9	9p13	Fanconi anaemia		+	[7]
FANCI	15q25-26	Fanconi anaemia		+	[7]
FANCJ/BRIP1	17q22.3	Fanconi anaemia		+	[7]
FANCL	2p16.1	Fanconi anaemia		+	[7]
FANCM	14q21.3	Fanconi anaemia		+	[7]
FANCN/PALB2	16p12.1	Fanconi anaemia		+	[7]
RECQL4	8q24.3	Rothmund-Thomson syndrome	+	+	[2,7]
C16orf57	16q13	Rothmund-Thomson syndrome	+	+	[2,7]
DKC1	Xq28	Dyskeratosis congenita		+	[7]
TERC	3q26.2	Dyskeratosis congenita		+	[7]
TINF2	14q12	Dyskeratosis congenita		+	[7]
TERT	5p15.33	Dyskeratosis congenita	+	+	[7,30]
RTEL1	20q13.33	Dyskeratosis congenita		+	[7]
NHP2	5q35.3	Dyskeratosis congenita		+	[7]
NOP10	15q14	Dyskeratosis congenita		+	[7]
WRAP53	17p13.1	Dyskeratosis congenita		+	[7]
CTC1	17p13.1	Dyskeratosis congenita		+	[7]
ACD	16q22.1	Dyskeratosis congenita		+	[7]
BLM/RECQL3	15q26.1	Bloom syndrome	+	+	[2,7]
WRN/RECQL2	8p12-11.2	Werner syndrome	+	+	[2,7]
TGRBR1	9q22.33	Multiple self-healing squamous epithelioma		+	[7]
Unknown	4q23	Huriez syndrome		+	[7]
MLH1	3p22.2	Muir-Torre syndrome	+	+	[2]
MSH2	2p21	Muir-Torre syndrome	+	+	[2]
MSH6	2p16.3	Muir-Torre syndrome	+	+	[2]
PMS2	7p22.1	Muir-Torre syndrome	+	+	[2]
PTCH1	9q22.32	Basal cell nevus syndrome	+		[2]
PTCH2	1p34.1	Basal cell nevus syndrome	+		[2]
SUFU	10q24.32	Basal cell nevus syndrome	+		[2]
Unknown	Xq25-27.1	Bazex-Dupré-Christol	+		[2]
MC1R (R and r variants)	16q24.3 V60L; V92M; R151C; I155T; R160W; D294H	–	+	+	[31–33]
HERC2/OCA2	15q13 rs12916300, rs1800407	–	+	+	[31,32,34]
TYR	11q14 rs1126809	–	+	+	[31,32,34]
IRF4	6p25 rs12203592	–	+	+	[31,32,34]
EXOC2	6p25 rs12210050; rs7335046	–	+	+	[32,33]
DEF8	16q24 rs4268748, rs8063761	–		+	[34,35]
ST3GALI	8q24.22 rs9643297	–		+	[35]
SRC	20q11.23 rs754626	–		+	[35]
ERBB2IP	5q12.3 rs17247181	–		+	[35]
PARK2	6q26 rs9689649	–		+	[35]
SLC45A2	5p13.3 rs16891982, rs35407	–	+	+	[31,32,34,36]
ASIP/RALY	20q11 rs6059655	–	+	+	[31,32,34]
FOXP1	3p13 rs62246017, rs2116709	–	+	+	[32,34]
HLA-DQA1	6p21 rs4455710, rs9276542	–	+	+	[32,34]
HLA-B	6p21.33 rs1050529	–	+		[32]

(*continued on next page*)

Table 1 (*continued*)

Gene	Locus/rs number	Condition	BCC	SCC	References
TPRG1/TP63	3q28 rs6791479	–		+	[34]
BNC2/CNTLN	9p22.2 rs74664507, rs10810657	–	+	+	[31,32,34]
CADM1	11q23.3 rs74899442	–		+	[31]
AHR	7p21.1 rs117132860	–		+	[31]
SEC16A	9q34.3 rs57994353	–		+	[31]
UBAC2	13q32.3 rs7335046	–	+	+	[33,35]
Unknown	2p22.23 rs192481803	–		+	[31]
Unknown	1p36 rs7538876	–	+		[37]
Unknown	1q42 rs801114	–	+		[37]
LPP	3q28 rs191177147	–	+		[32]
CUX1	7q22.1 rs73183643	–	+		[32]
ZBTB10	8q21.13 rs11993814	–	+		[32]
LINC00111	21q22.3 rs2775353	–	+		[32]
PLIN3	19p13.3 rs10425559	–	+		[32]
TNS3	7p12.3 rs7776701	–	+		[32]
NEU1	6p21.3 rs9267650	–	+		[32]
OBFC1	10q24.3 rs7907606	–	+		[32]
MIR3939	6q27 rs4710154	–	+		[32]
CASC15	6p22.3 rs2294214	–	+		[32]
TGM3	20p13 rs214785	–	+		[32]
RCC2	1p36.13 rs57142672	–	+		[32]
GATA3	10p14 rs73635312	–	+		[32,38]
CLPTM1L	5p15.33 rs421284	–	+		[32]
ALS2CR12	2q33.1 rs2080303	–	+		[32]
RHOU	1q42.13 rs61824911	–	+		[32]
RGS22	8q22.2 rs141115006	–	+		[32,39]
ZFHX4	8q21.11 rs10093547 rs28727938	–	+		[32,38]
CDKN2B	9p21 rs7874604 rs2151280	–	+		[32,36]
KRT5	12q13.13 rs11170164	–	+		[32,36]
TP53	17p13.1 rs78378222	–	+		[32,40]
MYCN	2p24 rs57244888	–	+		[38]
TGM3	rs214782	–	+		[39]
KLF14	7q32 rs157935	–	+		[36]
TERT-CLPTM1L	rs401681	–	+		[36]

Genetic epidemiology

Nearly all BCCs have constitutive activation of the Hedgehog signalling pathway, usually due to a loss of heterozygosity, generally of chromosome 9q, or an inactivating mutation in the *PTCH1* gene, also located on 9q. Where *PTCH1* is intact, activating mutations in *SMO* are usually present. Inactive *PTCH1* or activated *SMO* lead to elevated expression of GLI transcription factors, which appears to be necessary for BCC formation. Approximately 50% of BCCs also have mutations in *TP53*, usually with a UV signature. Microdissection and gene amplification studies show that BCCs are monoclonal proliferations that form into multi-centric, subclonal tumours [2,4]. BCCs in general have the greatest number of mutations of any human cancer, possibly because of their association with the ubiquitous mutagen UV radiation. This high mutation rate may lead to increased antigenicity and high immunosurveillance, leading to the slow growth and low metastatic potential of BCCs [2].

UV-mediated models of SCC most commonly have *TP53* mutations. Generally one *TP53* allele is deleted, while the second carries a missense mutation, usually with a UV signature. *TP53* mutations appear very early in the carcinogenesis of SCC and can be found in actinic keratoses, SCC in situ and invasive SCCs. *NOTCH1* or *NOTCH2* have loss-of-function mutations in 75% of cutaneous SCCs. The *CDKN2A* locus also often contains a mutation or epigenetic silencing, and approximately 50% of SCCs in immunocompromised patients have amplification of the oncogene *c-Myc*. Approximately 20% of SCCs have point mutations in *KNSTRN*, important for chromosome segregation. Loss of heterozygosity occurs frequently in SCCs and actinic keratoses, but unlike BCCs the deletions occur in several chromosomes, most frequently in chromosome 9p and 3p. While chemical models of SCC in mice usually have an activating mutation in *HRAS*, this is not commonly found in human SCCs or in a UV-induced SCC mouse model [4].

SCCs form from a single keratinocytic cell that has undergone mutation and transformation, progressing from p53 clone precursors to mild squamous cell dysplasia, through to severe dysplasia, SCC in situ and then invasive SCC, through the gradual acquisition of extra genetic mutations that add to the cells' selective growth advantage. Actinic keratosis and Bowen disease are recognised precursor lesions that display mild to severe squamous cell dysplasia [4].

Imaging methods: Dermoscopy

Dermoscopy of BCC is a well-known and useful imaging modality, with magnification and either polarised light or a contact gel or liquid allowing the user to see structures in the upper layer of the skin more clearly (Fig. 1). BCCs of the head and neck retain most of the dermoscopic signs of BCCs elsewhere on the body [11]. Branched (arborizing) vessels in sharp focus are the hallmark of BCCs (Fig. 1A), especially on the face, but are significantly less common on the scalp. Smaller fine branched vessels and a scattered vascular pattern, where blood vessels are distributed haphazardly throughout the lesion, are particularly common in superficial BCCs; corkscrew vessels are present in about 50%. Ulceration, micro-ulcerations, and shiny white (crystalline), milky pink or red areas are also common in superficial BCCs; these structures are more easily seen with polarised light dermoscopy, and shiny white structures are only visible under polarised light (Fig. 1C and D). Ulcerations are more common on the face than elsewhere on the body [12–14].

Pigmented BCC contain extra dermoscopic structures representing free melanin, melanin in basal cells or melanocytes within the basaloid tumour islands (Fig. 1B). Pigmented structures are particularly common in BCCs on the scalp, and less so on the face [14]. Blue-grey or brownish structureless zones (blotches), brown lines connected to a common base (leaf-like structures), or radial lines converging on a central dot or clod

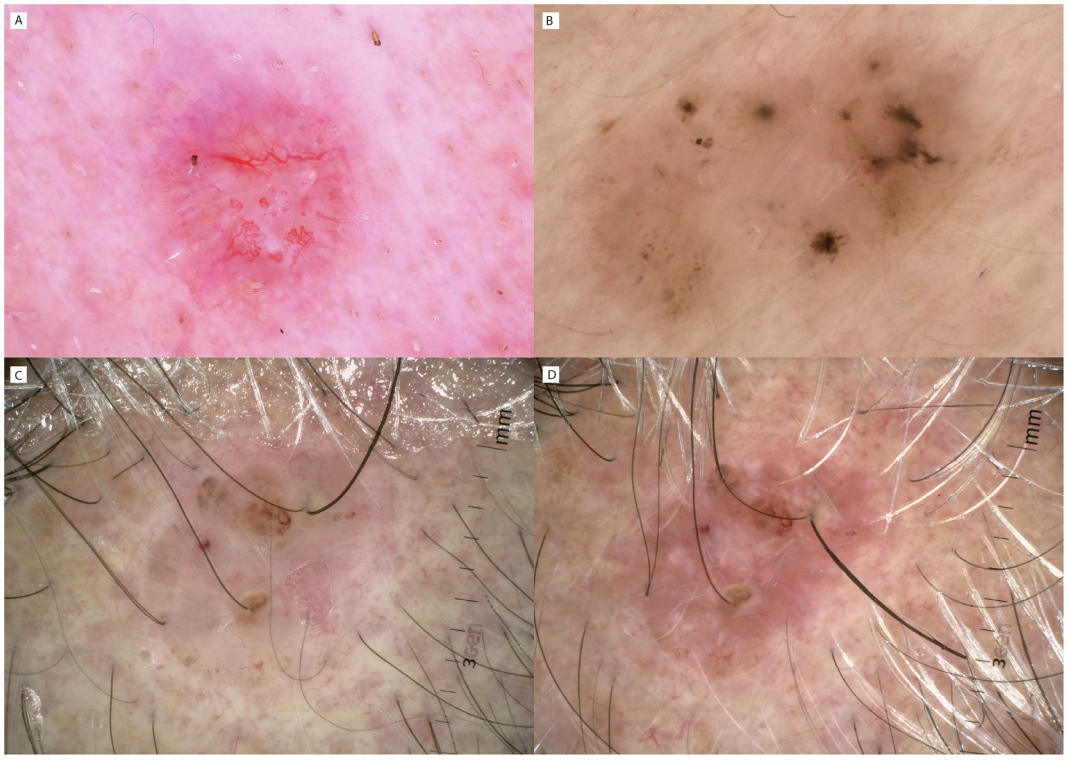

Fig. 1. Dermoscopy of basal cell carcinoma. (A) A facial BCC showing the classic sharply in-focus branched (arborizing) vessels. (B) A pigmented BCC with radial lines converging on a central dot (spoke-wheel areas), brown blotches, and gray and brown dots. (C) A pigmented BCC on a severely sun-damaged scalp, imaged with gel contact dermoscopy. (D) The same BCC imaged with polarized light dermoscopy, revealing the shiny white structures and showing fine vessels that had been blanched in the previous image by the contact pressure. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(spoke-wheel structures) are common signs of a pigmented BCC. More rarely, they may have brown to black dots and globules or blue-white veil. Heavily pigmented, dark blue BCCs can be indistinguishable from melanoma without histology; however, BCCs never have reticular lines (pigment network) or brown structureless zones interrupted by follicles (pseudonetwork) [1,11,13,14]. Menzies et al proposed a model for diagnosing pigmented BCCs that requires the lesion to have no reticular lines AND at least one of: branched (arborizing) vessels, ulceration, clustered, oval blue-grey clods (ovoid structures), multiple blue-grey dots or clods, leaf-like structures or spoke-wheel structures. This model has a sensitivity of 97% and specificity of 92–93% [15].

As with BCCs, dermoscopy is a useful tool for diagnosing SCC and its precursor lesions (Fig. 2); however, heavy scaling present in some SCCs can obscure underlying structures and should be wiped away where possible. The appearance of blood vessels under dermoscopy is the main clue to SCCs, with red dots (dotted), straight or serpentine (linear-irregular), and looped (hairpin) vessels, or a combination of these forms, typically present; on the face, red dots (dotted) or coiled (glomerular) vessels clustered into foci are common [1,5,11]. A whitish halo around the vessels is common to many keratinising lesions including SCC and KA, and helps distinguish these from polymorphic vessels in melanoma. Other dermoscopic signs of SCC are red, brown or black structureless zones (blotches), representing ulceration and crusting, and white circles (targetoid hair follicles). A scaly surface, homogenous blue pigmentation, and blue-grey dots (granular structures) are common in pigmented SCCs [1,13,16]. Poorly differentiated SCC is more likely to be predominantly red in colour, have bleeding or have vessels in more than 50% of the lesion's surface, while moderately- or well-differentiated SCC is more likely to be white or yellowish with scale [17].

The main dermoscopic sign of a facial AK, in more than 90% of cases, is a pink or red structureless zone interrupted by hair follicles, which are either white or filled with yellowish keratotic plugs, called a strawberry pattern (Fig. 2A); in contrast, elsewhere on the body AKs usually have surface scaling and red dot (dotted) vessels. Facial AKs and thin SCCs can also have rosettes, a cluster of four white circles in a square, which are only visible under polarised light. Linear or wavy vessels are sometimes seen around the follicles, and Bowenoid AK typically has coiled (glomerular) vessels distributed regularly [1,5,16]. Pigmented AKs on the face often have a brown structureless zone interrupted by keratin-filled follicles (pseudonetwork) (Fig. 2B). They can also have melanoma-like features, such as asymmetrically-pigmented follicular openings, polygonal lines (rhomboids or zigzag lines), and grey dots and granules. Clues pointing to AK rather than melanoma include a rough texture, fine scale, sharply-demarcated scalloped (moth-eaten) borders, thin curved parallel brown lines (fingerprinting), and fine interrupted lines; however it may be impossible to distinguish a pigmented AK from a lentigo maligna without histopathology [11,13,16].

Non-pigmented forms of SCC in situ (Bowen disease) are reliably diagnosed by the combination of surface scale, usually in the centre of the lesion, and coiled (glomerular) vessels in focal clusters; these features have a 98% diagnostic probability of SCC in situ. Pigmented forms are more common on darker skin types, and often have surface scale, brown or grey dots arranged in radial lines at the lesion periphery, skin coloured or pink structureless areas, grey-brown structureless areas interrupted by follicles (pseudonetwork) and coiled (glomerular) vessels in clusters, in radial lines, or arranged randomly [5,16].

Keratoacanthoma (Fig. 2E) has a structureless central yellow or brownish mass of keratin, surrounded by elongated or thick telangiectasias. Vessels may be looped (hairpin), serpentine or branched serpentine (linear-irregular), often surrounded by white or yellow halos. As with other SCC forms, coiled (glomerular) vessels are often present [16].

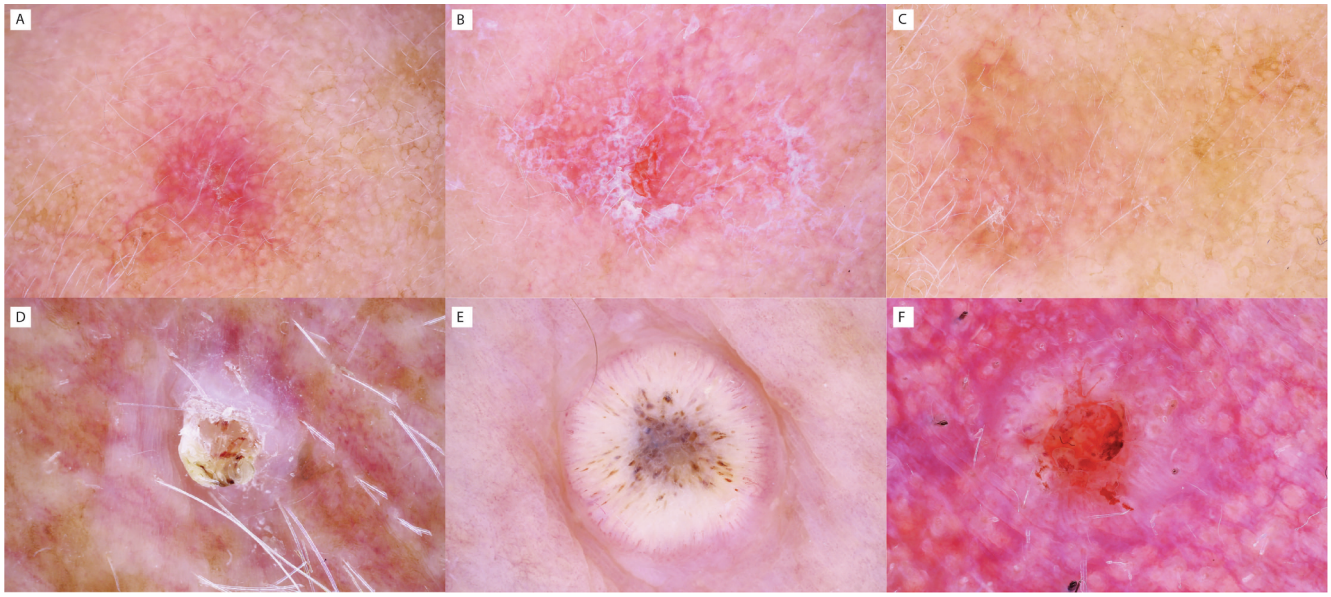

Fig. 2. Dermoscopy of squamous cell carcinoma and precursors. (A) An AK on the cheek showing the characteristic strawberry sign: a pink structureless area interrupted by white follicular openings. (B) A hypertrophic AK on the face with heavy scaling and a zone of ulceration. (C) A pigmented AK on the cheek with brown structureless areas interrupted by follicular openings. On the left are asymmetrically pigmented follicular openings, a potential sign of lentigo maligna, but the scaling on the lower left and centre point to an AK. (D) An SCC in situ in heavily sun damaged skin on the neck, with a keratotic horn, pink structureless zones and irregular vessels. (E) A keratoacanthoma with a brownish keratin-filled centre, surrounded by looped and linear vessels near the periphery. (F) An invasive SCC on the cheek with red areas of ulceration and looped and linear irregular vessels surrounded by a whitish halo. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Imaging methods: Reflectance confocal microscopy

Reflectance confocal microscopy (RCM) is a non-invasive diagnostic modality, allowing horizontal imaging of layers of the epidermis and dermis at quasi-histological resolution up to a depth of 250 μm. This is particularly useful on the head and neck, where it allows for in vivo assessment and diagnosis of cutaneous lesions, potentially avoiding surgical interventions in anatomically hazardous and cosmetically sensitive areas. In addition, handheld RCM devices can be used to perform in vivo mapping of larger lesions in order to optimise accurate clinical excision margins. This allows for reduced repeat excisions and aids in tissue conservation [18].

Under RCM, BCC display a variety of features, with the most prominent diagnostic features typically occurring at the dermoepidermal junction (DEJ) and within the papillary dermis (Fig. 3). At the DEJ, BCCs present as hyporeflective tumour islands, in either an oval, polycyclical or elongated pattern, outlined by bright collagen bundles (dark silhouettes) (Fig. 3B and D) and are surrounded by dark cleft-like hyporeflective spaces, representing mucinous oedema (Fig. 3C). Tightly-packed cells in the papillary dermis form a nodular or cord-like pattern, and palisading of tumour cell nuclei can be seen.

Architectural disarray of various types is also found in the epidermis. Branching blood vessels, seen as large, linear dark spaces that split into narrower dark spaces, have a high predictive value (78.6%) for BCC, followed by straight linear (69.6%) and tubular vessels (67.9%) [19].

Pigmented BCCs may also have bright dendritic cells within the tumour islands, along with melanophages, appearing as bright oval or plump triangular cells with an indistinct nucleus. In these cases, elongated monomorphic nuclei, aligned along the same axis, may form a streaming pattern [1,20,21].

Many of the above features are present even in lesions that are clinically and dermoscopically featureless or that mimic melanoma, highlighting RCM's effectiveness in equivocal lesions [22,23]. However, infiltrative BCCs remain challenging to diagnose with RCM, because the strands of neoplastic cells are difficult to see among strands of dermal collagen, and deeper structures are still out of reach for RCM visualisation [21].

When used to examine any suspicious lesion that might be a BCC, RCM sensitivity is 76% (95%CI 45–92%), while specificity is 95% (95%CI 66–99%). When used for equivocal lesions, where clinical and/or dermoscopic assessment could not provide a clear management decision, sensitivity was 94% (95%CI 79–98%) and specificity was 85% (95%CI 72–92%), highlighting RCM's potential as a second-line assessment device [20]. A study comparing diagnosis of 260 pink cutaneous lesions, including 114 BCCs, with dermoscopy and RCM found they had comparable sensitivity (85.1% for both) and specificity (92.4% and 93.8%, respectively) [24].

Unlike BCC, relatively few studies have examined large numbers of SCCs with RCM, so information differentiating AK, SCC in situ and invasive SCC is limited. Currently available data suggests that sensitivity ranges from 74 to 77% and specificity from 92 to 98% [20]. As with dermoscopy, surface scaling can obscure underlying structures, and parakeratosis (subsurface scale) also appears as amorphous, highly refractile structures in the stratum corneum [1,25].

AK shows a thickened and irregular stratum corneum, with dark nuclei and bright, amorphous areas of parakeratosis. Further into the stratum granulosum and spinosum, there can be an irregular honeycomb pattern caused by pleomorphic cells that vary in size, shape and how crowded together they are, with lines varying in thickness and brightness, and dark nuclei of varying sizes. Wide, clumped collagen bundles, representing solar elastosis, are often seen in the papillary dermis, due to these lesions' location on sun-damaged skin. Small, bright dots, representing inflammatory cells, may also be present, and in pigmented AK there can also be a ring of pigmented keratinocytes around hair follicles and plump, bright cells in the dermis [21,26]. As photodamaged skin shares some confocal features with AK, principally an atypical honeycomb pattern and some parakeratosis, clinical and dermoscopic features are needed to prevent over-diagnosis [27,28].

SCC in situ also present an irregular honeycomb pattern, along with targetoid cells, either with a bright centre and peripheral dark halo, or with a dark centre, bright rim and dark peripheral halo. Blood vessels in

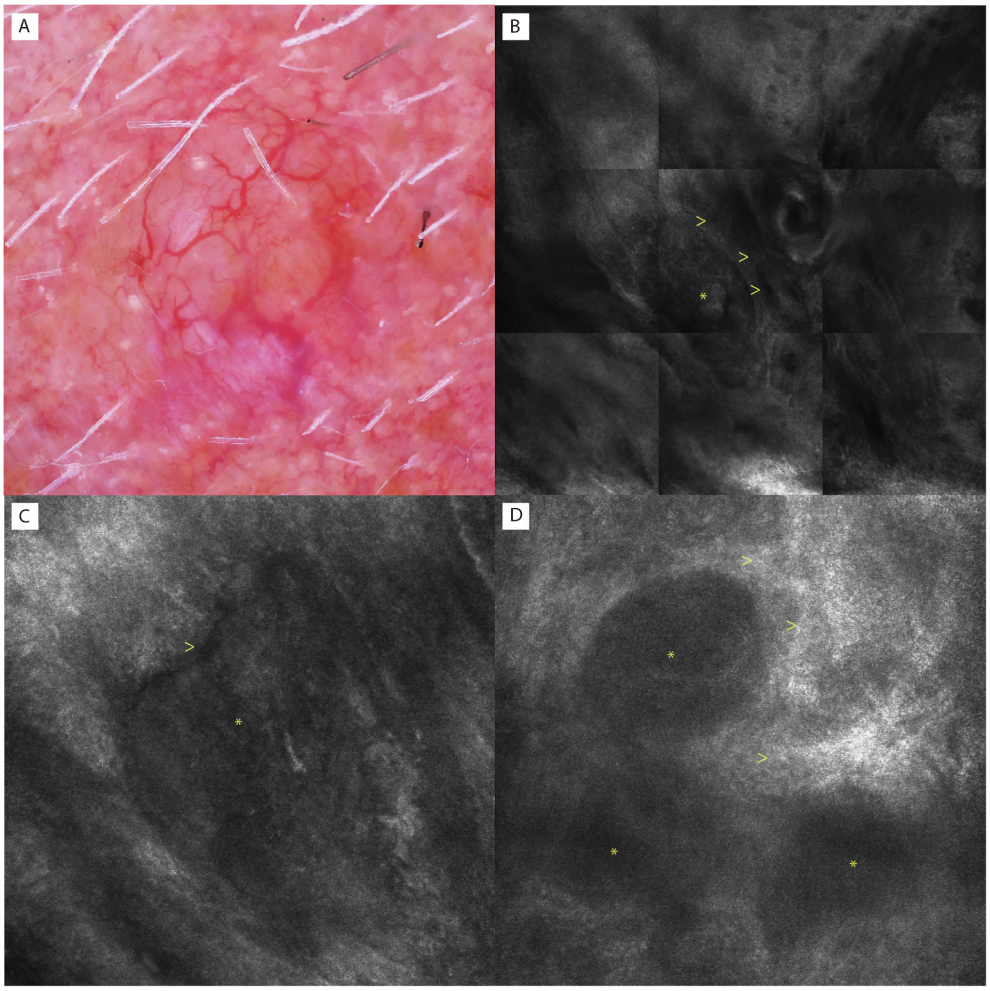

Fig. 3. Reflectance confocal microscopy of a basal cell carcinoma. (A) Dermoscopic image of the nodular BCC on the neck. (B) An RCM mosaic (1.5 mm × 1.5 mm) at the dermoepidermal junction showing basaloid tumor islands (asterisk) surrounded by thick collagen (arrows). (C) RCM image (0.5 mm × 0.5 mm) at the dermoepidermal junction showing a tumor island (asterisk) with clefting (arrow). (D) RCM image (0.5 mm × 0.5 mm) at the dermoepidermal junction showing dark silhouettes of basaloid tumor islands (asterisks) surrounded by bright thick collagen (arrows).

the superficial papillary dermis are round or oval shaped, and in the lower papillary dermis they become s-shaped. Pigmented versions also have dendritic cells in the epidermis, plump, bright cells in the dermis, and brightly-edged papillae at the dermo-epidermal junction [5,25,26,29].

SCCs usually have more pronounced versions of the RCM features of AK and SCC in situ. Erosion or ulceration is often evident. The irregular honeycomb pattern in the epidermis can disintegrate in places into a disarranged pattern, and more targetoid cells with a dark centre and bright rim can be seen. In the papillary dermis, there are often dark circles or ovals representing dilated blood vessels, running perpendicularly to the plane of imaging. Nest-like structures and speckled cells with a dark nucleus may be present in the dermis [5,21,29]. Poorly-differentiated SCC are characterised by architectural disarrangement, while well-differentiated SCC have a better-preserved overall architecture and are more likely to have speckled cells in the epidermis [29].

Conclusion

Keratinocyte cancers are the most common malignancy among people with European ancestry, and while they have low rates of metastases, they can cause significant morbidity, with lesions commonly appearing on sun-exposed areas of the head and neck. While there are a variety of genetic, environmental and occupational risk factors for both BCC and SCC, UV exposure is the most common risk factor. Dermoscopy is a well-established diagnostic tool for BCC, SCC and precursor lesions, while RCM is emerging as another useful diagnostic tool, particularly for head and neck lesions, where it allows for in vivo assessment that potentially avoids surgical interventions in anatomically and cosmetically sensitive areas and optimises accurate clinical excision margins.

Declaration of Competing Interest

HPS is a shareholder of MoleMap NZ Limited and e-derm consult GmbH, and undertakes regular teledermatological reporting for both companies. HPS is a Medical Consultant for Canfield Scientific Inc., a Medical Advisor for First Derm, and has a Medical Advisory Board Appointment with MoleMap NZ Limited. HPS holds an NHMRC MRFF Next Generation Clinical Researchers Program Practitioner Fellowship APP1137127. KJL: none declared.

Acknowledgements

The authors would like to thank Dr Mitchell Robinson for his assistance with the RCM images.

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