Epidemiology of basal cell carcinoma: scholarly review

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ABSTRACT

Basal cell carcinoma (BCC) is the most common cancer in white-skinned individuals with increasing incidence rates worldwide. Patients with BCC place a large burden on healthcare systems, because of the high incidence and the increased risk of synchronous and metachronous BCCs and other ultraviolet radiation (UVR) related skin cancers (i.e., field cancerization). As a result, the disability-adjusted life years and healthcare costs have risen significantly in recent decades. BCC is a complex disease, in which the interplay between UVR, phenotype (UVR-sensitive) and genotype (somatic mutations and germline mutations/polymorphisms) fulfils a key role in the aetiopathogenesis. Prevention programmes with continual refinements and improvements could be of major importance in tackling the growing skin cancer problem. To provide the most appropriate BCC care, physicians should engage in shared decision-making and choose their treatments wisely.

INCIDENCE, TRENDS AND GEOGRAPHIC DIFFERENCES

Basal cell carcinomas (BCCs) do not have a precursor lesion and most likely arise from stem cells within hair follicles and interfollicular epidermis.[1,2] There are different histopathological subtypes, of which nodular is the most frequent, followed by superficial and infiltrative, and mixed types are frequently found as well.[3–5] The frequencies reported depend on the classification system used and period.[3,6] Most BCCs occur in the head and neck region (i.e., sun exposed), followed by trunk and extremities (i.e., relatively sun-unexposed).[3,4]

Incidence per region, trends and differences

BCC is the most common cancer in white-skinned people with increasing incidence rates worldwide.[7] Although reliable BCC incidence estimates are needed to monitor trends and allocate healthcare services, it is remarkable how few countries register BCCs in national/regional cancer registries. This registration gap can be explained by the tumour's high volume and low mortality, along with an inability to include nonhistopathologically confirmed BCCs and high incidence of synchronous and metachronous BCCs.

Comparisons of incidence rates between countries is difficult because different standardization methods are used. The incidence of BCC is strongly inversely related to the country's geographic latitude combined with the pigment status of its inhabitants (Table 1). The rates in Europe have increased approximately 5% annually over recent decades.[7] In the U.S.A., rates have increased about 2% per year leading to over 2.5 million patients with BCC treated annually.[7–9] The highest rates are seen in Australia, where over one in two inhabitants will be diagnosed with BCC by the time they are 70 years old, but the increasing incidence in Australia appears to be reaching a plateau, as the rates for people below 60 years of age have stabilized.[7,10,11] In non- Western regions, such as Asia and South America, incidence rates are ten to hundred-folds lower, but have also increased.[12,13]

The increase in incidence can be explained by an increased awareness in the general population and among physicians, more surgical treatments (e.g., more excisions with histopathological confirmation instead of cryotherapy or electrodessication), improved registration, an ageing population and changes in the distribution of risk factors such as ultraviolet radiation (UVR) exposure patterns. The latter is often a matter of debate, but is underlined by the observation that the incidence of UVR-related skin tumours increased significantly and more steeply compared with other cutaneous malignancies.[14]

BCC incidence increases significantly with age, but the most remarkable increase has been observed in young women in both Europe (Netherlands and Denmark) and the U.S.A., resulting in a reversed male : female ratio (female > male) in younger

Table 1. Overview of incidence rates and trends of BCC worldwide

Continent	Country	Latitude[a]	Incidence rate[b]	Standardization	Period[c]	Trends (EAPC)	Reference
Europe	Finland	61° N	♀90.2; ♂104.8	ESR	2009	-	De Vries, 2012[200]
	Scotland	56° N	♀81; ♂123	ESR	2006	-	De Vries, 2012[200]
	Denmark	56° N	♀96.6; ♂91.2	WSR	1978-**2007**	♀4.6%; ♂3.7%	Birch-Johansen, 2010[16]
	Lithuania	55° N	♀47.4; ♂46.4	ESR	1996-**2010**	♀2.6%; ♂3.3%	Jurciukonyte, 2013[201]
	United Kingdom	55° N	♀135.4; ♂172.1	ESR	2000-2011	-	Reinau, 2014[202]
	Northern Ireland	54° N	86.8	ESR	2000-2006	-	Lomas, 2012[7]
	Ireland	53° N	♀85.7; ♂98.0	WSR	1994-2003	-	Carsin, 2011[203]
	England	52° N	76.2	ESR	2000-2006	-	Lomas, 2012[7]
	Netherlands	51° N	♀157.3; ♂164.7	ESR	2002-**2009**	♀7.9%; ♂6.8%	Flohil, 2013[17]
	Germany	51° N	82.2	ESR	2006-**2010**	6.8%	Rudolph, 2015[204]
	Croatia	45° N	♀24.5; ♂33.6	WSR	2003-2005	-	Lipozenčić, 2010[205]
	Serbia	44° N	♀27.8; ♂31.0	WSR	1999-**2011**	6.1%	Videnović 2015[206]
	Spain	41° N	128.0	WSR	2006-2007	-	Bielsa, 2009[207]
	Malta	35° N	♀70; ♂84	ESR	2009	-	De Vries, 2012[200]
North America	Canada (AB)	53° N	♀119.6; ♂147.0	CAN	2000-**2006**	-0.8%	Jung, 2010[208]
	Canada (MB)	53° N	♀77.4; ♂93.9	WSR	1971-**2000**	2.4%	Demers, 2005[209]
	USA (NH)	43° N	♀165.5; ♂309.9	USA	1979-1980, **1993-1994**	♀4.4%; ♂4.4%	Karagas, 1999[210]
	USA	37° N	♀1,019; ♂1,488	ASR	2004-**2006**	-	Wu, 2013[211]
	USA (CA)	36° N	♀774; ♂1,069	USA	1998-**2012**	0.9%; ♀1.1%	Asgari, 2015[100]
	USA (NM)	34° N	♀485.5; ♂930.3	USA	1998-1999	-	Athas, 2003[212]
	USA (AZ)	34° N	♀497.1; ♂935.9	USA	1996	-	Harris, 2001[213]
Asia	Jordan	33° N	♀8.8; ♂6.2	WSR	1991-2000	-	Rawashdeh, 2004[12]
	Israel	31° N	♀158; ♂225	ESR	2006-2011	-0.7%	Sella, 2015[214]
	Singapore	1° N	4.5	-	2003-2006	-	Sng, 2009[215]

Table 1. Overview of incidence rates and trends of BCC worldwide (*continued*)

Continent	Country	Latitude[a]	Incidence rate[b]	Standardization	Period[c]	Trends (EAPC)	Reference
Africa	Kenya	0°	0.0065[d]	CIR	1968-1997	-	Munyao, 1999[216]
	South Africa	30° S	♀1.7[d]; ♂3.0[d]	ASR	2000-2004	-	Norval, 2014[217]
South America	Brazil	27° S	295.2	CIR	2008	-	Custódio, 2010[218]
	Chile	53° S	3.9	CHL	1994-2000	-	Abarca, 2002[13]
Oceania	Papua NG	6° S	0.3	CIR	1960-1980	-	Foster, 1988[219]
	Australia	25° S	♀745; ♂1,041	WSR	2002	-	Staples, 2006[10]
	Australia (QLD)	26° S	♀1,269; ♂1,813	WSR	1997-2006	-	Richmond-Sinclair, 2009[220]
	New Zealand	40° S	♀215; ♂383	WSR	1997-2006	♀4.4%; ♂3.1%	Brougham, 2011[221]

BCC, basal cell carcinoma; EAPC, estimated annual percentage change; ESR: European Standardized Rate; WSR: World Standardized Rate; AB, Alberta; CAN: Canadian standardized rate; MB, Manitoba; USA (country), United States of America; NH, New Hampshire; USA, USA standardized rate; ASR, Age Standardized Rate; CA, California; NM, New Mexico; AZ, Arizona; CIR: Crude Incidence Rate; CHL: Chile standardized rate; Papua NG, Papua New Guinea; QLD, Queensland.

[a] Estimate (rounded) of the latitude (N, Northern Hemisphere; S, Southern Hemisphere), based on latitudes from www.worldatlas.com (visited at 18-04-2016).

[b] Per 100,000 person years, both sexes combined or separated.

[c] The year(s) represent the period to which the incidence rates belong, if in **bold**, the incidence rate belongs to that specific year.

[d] Incidence rate for native Africans.

populations compared with older populations (male > female).[15–17] This discrepancy between men and women could be a result of the higher use of tanning beds by young women[18,19] and of women paying closer attention to their appearance and the health of their skin, which may result in more medical visits.[20]

Multiple basal cell carcinomas

In line with the concept of field cancerization,[21] patients diagnosed with a first BCC have an increased risk of developing a second BCC and other UVR-related skin cancers.[22,23] Patients with a BCC have a 17-fold increased risk of a subsequent BCC compared with the general population, followed by a threefold increased risk of a subsequent squamous cell carcinoma (SCC) and a twofold increased risk of a melanoma.[23] The majority of patients with skin cancer are prone to develop the same type (i.e., BCC or SCC) of skin cancer.[24] Approximately one-third of all patients with a first BCC will develop at least a second BCC, 4% an SCC and 0.5% a melanoma, but these elevated risks also vary geographically and reflect the underlying incidence rates.[23] The likelihood of subsequent UVR-related cancers supports the concept that skin cancer shows similarities with other chronic conditions, something which has been coined 'actinic neoplasia syndrome' by Weinstock et al.[25]

BURDEN OF DISEASE

Global skin cancer burden

The World Health Organization (WHO) quantifies the burden of a disease with the disability-adjusted life year (DALY).[26] This time-based measure aggregates years of life lost through premature death (YLL) and years lived with disability (YLD). One DALY equals the loss of 1 year of life lived in full health.

The mortality of BCC is extremely low as it rarely metastasizes, with rates ranging from 0.0028% to 0.55%, and will therefore hardly affect YLL.[27] However, the high and increasing BCC incidence, the decreasing age at first BCC, and the high occurrence of multiple BCCs (mBCC) and other UVR-related skin cancers puts a strain on healthcare services. The WHO Global Burden of Disease (GBD) project showed that the age-standardized YLD rates for nonmelanoma skin cancers (NMSCs) increased significantly between 1990 and 2013 (42.5%, to 126 200) and are comparable with the rates of oesophageal, ovarian or thyroid cancer.[28] Unfortunately, the GBD project does not differentiate between the various NMSC subtypes.

A GBD on UVR exposure computed a BCC-specific DALY and estimated that 58 000 DALYs were lost globally in 2000.[29] A Dutch study of keratinocyte cancer (KC; both BCC and SCC) burden showed that the world standardized DALY rates for BCC

in both sexes doubled between 1989 and 2008, from two to four per 100 000 person-years.[30] However, both studies included only the first BCC and therefore will have underestimated the true burden.

Healthcare costs

Results of cost analysis studies of different BCC treatments are usually not generalizable, because of the different healthcare systems between countries. Nonetheless, a 2015 systematic review summarized the healthcare expenditure for different countries and national cost estimates were adjusted for country-specific inflation and presented in 2013 euros.[31] In absolute terms, the U.S.A. spends the most money on KC (~ 600 million), followed by Australia (> 350 million), Germany (> 150 million) and the U.K. (> 100 million).[31] However, the KC costs relative to the size of the population were highest for Australia, followed by New Zealand, Sweden and Denmark, whereas Brazil and Canada had the lowest.[31]

A U.S.A. Medicare expenditure study showed that NMSC was the fifth most costly cancer between 1992 and 1995.[32] One U.S.A. study estimated the productivity loss per BCC case and reported an estimated cost of $1235.[33] A recent report estimated the average annual cost of treating NMSC in the U.S.A. at $4.8 billion from 2007 to 2011, which is a 74% increase compared with the 2002–06 estimate.[34] A relatively large part of the U.S.A. treatment costs (> $2 billion) comprise Mohs micrographic surgery (MMS), a treatment which has grown exponentially in recent decades.[35,36] MMS is a cost-effective treatment as long as it is performed by skilled physicians and used in properly selected patients, such as patients with recurrent or aggressive histological BCCs in the H-zone (temporal, retro- and pre-auricular, orbital and infranasal areas, ears and nose).[35,37,38] From at least a cost perspective, usage of MMS should be monitored to prevent over-usage.

Another potential cost driver of BCC care is methylaminolaevulinate photodynamic therapy (MAL-PDT). In the Netherlands, MAL-PDT was used very frequently, in part due to a very profitable reimbursement.[39] This changed after a Dutch single-blind, noninferiority, randomized controlled trial (RCT) demonstrated that the much less costly topical fluorouracil and imiquimod were not inferior to MAL-PDT for clearance of superficial BCC after 12 months.[40,41]

RISK FACTORS

BCC is a complex disease because the likelihood of developing this tumour depends on the interplay between constitutional predisposition (genotypic and phenotypic characteristics) and subsequent exposure to environmental risk factors. Figure 1

shows the most important genetic, phenotypic and environmental risk factors for the development of BCC (see Supporting Information, Table S1, for more details). Because BCC is a complex disease, most risk factors studied have small effect sizes and it is very possible that several of the observed associations are false-positive and/or clinically irrelevant.[42]

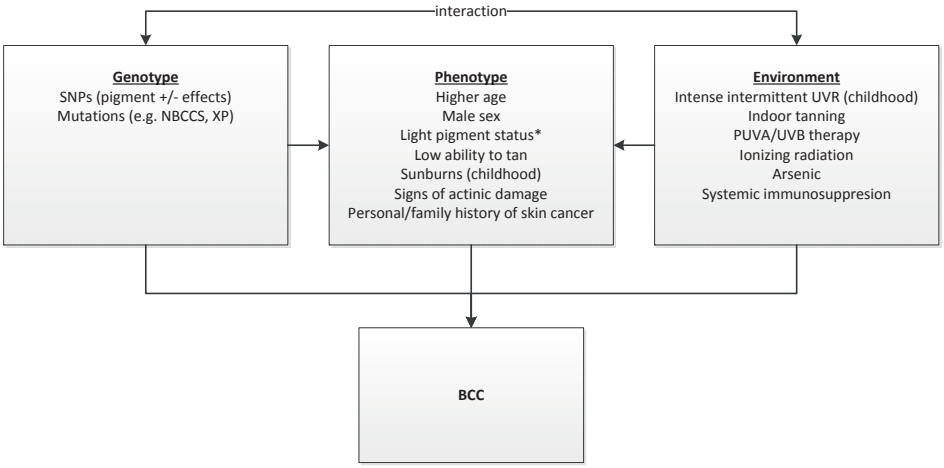

Figure 1. Main nongenetic risk factors of BCC
This flowchart shows the main genotypic, phenotypic and environmental risk factors for BCC. The arrows show how the different risk factor categories exert effects on each other and on BCC. BCC, basal cell carcinoma; SNPs, single nucleotide polymorphisms; NBCCS, naevoid basal cell carcinoma syndrome; XP, xeroderma pigmentosum; UVR, ultraviolet radiation; PUVA, psoralen plus ultraviolet-A radiation; UVB, ultraviolet B radiation. * Consists of complexion, hair colour and eye colour.

Complex disease: environmental risk factors

Ultraviolet radiation

UVR is the major environmental risk factor for BCC (population attributable fraction > 90%[43]), but its assessment is problematic (i.e., exposure pattern, timing and amount), its exposure varies but is universal and its effect sizes are small. Nevertheless, it seems that intense intermittent UVR exposure (e.g., outdoor recreational activities and beach holidays), in particular during childhood and adolescence, leads to a significant increase in the risk of BCC.[44–49] The amount of UVR exposure is positively associated with BCC risk, but this effect levels off or even decreases after a certain amount of exposure.[46,47] The skin's ability to tan modulates the UVR-induced risk.

A systematic review and meta-analysis showed that indoor tanning is significantly associated with an increased risk of BCC [relative risk 1.29; 95% confidence interval

(CI) 1.08–1.53; I^2 = 37%; no evidence of publication bias], especially if used early in life.[50] Patients with psoriasis who have had a high number (> 100–200) of psoralen plus UVA radiation (PUVA) treatments develop significantly more BCCs than expected and this risk seems to persist over time.[51–53] UVB therapy (> 300 treatments) has also been associated with modest risk increases in the risk of developing BCC.[51,54]

Photosensitizing drugs

Photosensitizing medication has the ability to induce a phototoxic and/or photo-allergic reaction upon UVR exposure. In addition to psoralen, other photosensitizing medications (e.g., diuretics, tetracyclines and nonsteroidal anti-inflammatory drugs) were shown to be positively associated with BCC in several pharmaco-epidemiological studies.[55–57] However, most of these studies suffered from important limitations and no dose–response relationships were observed.

Ionizing radiation

Patient groups at risk are those irradiated in the past for benign disorders such as tinea capitis, acne and otitis serosa,[58–61] and those irradiated for different types of cancer, including childhood cancer survivors and haematopoietic cell transplantation survivors.[62,63] Nonmedical groups at risk are atomic bomb survivors and occupational groups such as radiological technologists.[64,65] The elevated BCC risks are confined to the site of radiation exposure.[66]

Ionizing radiation (IR)-induced BCC risk appears to increase with a person's skin susceptibility to UVR and younger age at exposure (i.e., basal layer more sensitive to radiation carcinogenesis). [58,59,61] The development of mBCC in irradiated skin occurs frequently as well.[61]

Chemicals

Arsenic is a carcinogen that appears naturally (i.e., well water), medicinally and in the workplace (e.g., mining and agriculture).[67] Chronic exposure to arsenic can induce BCC formation, especially on the trunk, and BCC multiplicity occurs frequently as well.[67–69]

Smoking

A systematic review and meta-analysis showed that smoking is not significantly associated with BCC, with no evidence of publication bias [odds ratio (OR) 0.95; 95% CI 0.82–1.09; I^2 = 59%].[70] A less rigorous meta-analysis suggested that 'ever smokers' compared with 'never smokers' had slightly elevated risks of BCC (OR 1.02; 95% CI 1.00–1.04; I^2 = 84%).[71] Overall, it seems that smoking has little to no effect on BCC development.

Human papillomaviruses

In contrast to SCC, some observational studies have found a significant positive association between human papillomavirus (HPV) DNA or seropositivity and BCC.[72–74] However, most case–control studies did not find a clear association between different cutaneous oncogenic HPV types and BCC.[75–77] For now, the evidence that viral oncogenesis plays a role in BCC development is far from conclusive.[78]

Diet and drinks

The epidemiological literature on the role of dietary factors in the development of BCC is inconsistent and insufficient for most of the factors studied.[79] The evidence for protective effects of selenium, carotenoids and vitamins on BCC development is inconsistent.[80–84]

Several studies on the relationship between alcohol and BCC have been conducted, showing conflicting evidence and beverage-dependent relations.[85–89] Caffeine intake (e.g., coffee) has been associated with a reduced risk of BCC and mBCC.[90–92] Whether caffeine really inhibits photocarcinogenesis or is just a proxy for global health and lifestyle needs to be differentiated.[93]

Systemic immunosuppression

Over recent decades, the number of chronic immune-suppressed patients, who are at an elevated risk of SCC and to a lesser extent of BCC, has grown consistently as a result of the increasing number of organ transplant recipients, the immunosuppressive agents used in different diseases (e.g., inflammatory bowel disease and non-Hodgkin lymphoma) and the increased longevity of these chronic immune-suppressed patients.[94–96] The overall BCC incidence in renal transplant recipients was[7–16] (depending on geographic location) times greater than in the general population.[94,97,98] The extent of UVR exposure and UVR-induced DNA damage prior to transplantation (i.e., UVR-induced DNA mutations) combined with an impaired cutaneous immune surveillance results in an elevated field risk and metachronous BCCs and SCCs.[99]

Complex disease: phenotypic risk factors

Increasing age and male sex (at older age) are well-known host characteristics that increase the risk of BCC.[17,100] The ability to repair (UVR-induced) DNA damage reduces with age, which leads to an accumulation of damage and an increased incidence of BCC in older people.[101,102]

The highest BCC risks can be found in people with a personal and/or family history of skin cancer, who are (highly) sensitive to UVR exposure and are exposed to intense intermittent UVR. This sensitivity is determined by the combination of a fair complexion, light hair colour and light eye colour, and low ability to tan.[47–49,103–108]

Acute effects of excessive UVR exposure such as (childhood) sunburns and more long-lasting signs of actinic damage such as melanocytic naevi, freckles, solar elastosis, solar lentigines and actinic keratoses are also significant predictors of an increased BCC risk.[44,48,109–111] These manifestations of photodamage could be a warning sign of field cancerization.

Risk factors for different histopathological subtypes

Multiple observational studies have found body area, age and sex preferences for certain histopathological BCC subtypes (see Supporting Information, Table S1). Superficial BCCs are predominantly located on the trunk and patients diagnosed with a superficial BCC are significantly younger and more often female than patients with other subtypes.[3,4,6] These results could indicate that the different subtypes have other aetiologies with respect to UVR exposure and the interaction between constitutional characteristics and other environmental risk factors. In addition, truncal BCCs have been associated with acute intense intermittent exposure patterns.[112,113]

Risk factors for multiple basal cell carcinomas

Higher age at initial BCC, male sex and a history of BCC have all been found to be positively associated with metachronous BCCs (see Supporting Information, Table S1).[22,114,115] The value of other phenotypic (e.g., skin type) and environmental (e.g., UVR) characteristics in predicting a new BCC is under debate[22,114,116,117] and studies may be hindered by the index event bias.[118]

A recently developed prediction model for a second BCC showed that the risk factor profile differs between a first and second BCC.[92] The most discriminating predictor was the presentation of mBCC at first BCC diagnosis.[92] Other factors associated with a second BCC were age at first BCC (parabolic relation with maximum risk at 68 years), male sex, superficial subtype of the first BCC and coffee consumption.[92] An update of this prediction model, including up to five metachronous BCCs, is in preparation.

GENETIC PREDISPOSITION

Somatic mutations

UVR-induced cancers such as BCC and melanoma exhibit the highest prevalence of somatic mutations, of which the majority show 'UV signatures', of all cancers.[119,120] Acquired mutations in RAS oncogenes do not seem to play an important role in BCC pathogenesis.[121–123] However, two tumour suppressor genes are important in sporadic BCC carcinogenesis, namely patched 1 (PTCH1) and tumour protein p53 (TP53).

The key evidence of a crucial role of PTCH1 in BCC development came from patients with naevoid basal cell carcinoma syndrome (NBCCS). PTCH1 (chromosome 9q22) encodes a protein that is the receptor for sonic hedgehog, a secreted molecule implicated in the formation of embryonic structures and in tumorigenesis.[124,125] Loss of heterozygosity on chromosome 9q22 is the most frequent (58-69%) genetic alteration in sporadic BCCs.[126–128] Inactivation of PTCH1 and upregulation of hedgehog signalling are most likely pivotal events in BCC carcinogenesis.[129,130]

TP53 (chromosome 17p13) encodes a tumour suppressor protein that can induce several processes, such as cell cycle arrest, senescence, apoptosis and DNA repair.[131] Mutations in this gene play a role in carcinogenesis in a wide variety of tissues.[132] Direct DNA sequencing of the TP53 gene in BCCs revealed mutations in approximately 44–65% of tumours.[127,133,134]

Germline polymorphisms

The melanocortin 1 receptor gene (MC1R) is a major determinant of skin colour and hair colour, and MC1R variants are significantly associated with BCC risk, even after correcting for skin pigmentation.[135–137] This pleiotropy suggests that MC1R variants exert carcinogenic pigmentation independent effects. Pigmentation pathway single-nucleotide polymorphisms (SNPs) in tyrosinase (TYR) and agouti signalling protein (ASIP) confer risk of BCC as well.[138] Studies investigating a possible link between defects in DNA repair genes and BCCs have yielded conflicting results.[130]

The first genome-wide association study in patients with BCC was conducted in 2008 and since then, six have been performed in total, finding 17 different risk-increasing SNPs mapped to 16 different chromosomal regions (Table 2).[139– 144] The ORs found are small overall, between 1.15 and 1.55 (except for TP53 variants), and it is not surprising that much of the genetic variability is still unexplained. New approaches such as exome sequencing and epigenetic studies will further explain heritability.

The genetic predisposition of mBCC is not well documented and may involve genetic changes different from those associated with a primary BCC.[145] The cytochrome (CYP) supergene family and the glutathione S-transferase (GST) supergene family are involved in different metabolizing and detoxification processes, such as detoxification of products of oxidative stress.[146] Polymorphisms in these genes have been associated with increasing BCC numbers.[147–149]

Germline mutations

NBCCS is an autosomal dominant disorder characterized by mBCC, odontogenic keratocysts of the jaws, palmar and/or plantar pits and skeletal abnormalities.[150–152] The majority of patients with NBCCS start developing their BCCs from puberty onwards and affected individuals may develop from a few up to over a thousand BCCs.[150,151]

Patients exposed to IR or high levels of UVR become even more susceptible to BCC formation.[150,151] Using family-based linkage studies of NBCCS kindreds, the causative locus was first mapped to 9q22 and then to the PTCH1 gene.[124–126]

Patients suffering from xeroderma pigmentosum (XP) have germline mutations in their nucleotide excision repair genes, which are of crucial importance for removing UVR-induced DNA damage.[153] They have high risks of developing mBCC and other skin cancers during childhood.[154]

A few other genodermatoses can also cause development of mBCC early in life, namely Bazex Dupre–Christol syndrome[155,156] and Rombo syndrome.[157,158]

Table 2. Genome-wide significant risk SNPs for BCC[a]

SNP[b]	Risk allele	Frequency	Context	Region	Mapped gene[b]	OR (95% CI)
rs7538876	A	0.35	intron	1p36.13	PADI6	1.28 (1.19-1.37)
rs801114	G	0.33	downstream gene	1q42.13	RHOU, LOC105373143	1.28 (1.19-1.37)
rs401681	C	0.56	intron	5p15.33	CLPTM1L	1.25 (1.18-1.34)
rs7335046	G	0.12	downstream gene	13q32.3	UBAC2, LINC01232	1.26 (1.18-1.34)
rs1805007	T	0.07	missense	16q24.3	MC1R	1.55 (1.45-1.66)
rs12210050	T	0.17	intergenic	6p25.3	LOC105374875	1.24 (1.17-1.31)
rs78378222	C	NR	3′ UTR	17p13.1	TP53	2.16 (1.83-2.54)
rs214782	G	0.17	intron	20p13	LOC105372503, TGM3	1.29 (1.22-1.37)
rs7006527	A	0.86	intron	8q22.2	RGS22	1.3 (1.22-1.41)
rs59586681	T	0.61	intergenic	20p13	LOC388780	1.16 (1.11-1.22)
rs2151280	G	NR	intron	9p21.3	CDKN2B-AS1	1.2 (1.14-1.27)
rs157935	T	NR	intron	7q32.3	LINC-PINT	1.23 (1.15-1.31)
rs57244888	T	0.90	intergenic	2p24.3	LOC105373443, LOC105373444	1.32 (1.22-1.43)
rs13014235	C	0.46	missense	2q33.1	ALS2CR12	1.15 (1.10-1.20)
rs28727938	C	0.94	intron	8q21.13	LINC01111, MRPL9P1	1.43 (1.30-1.59)
rs73635312	G	0.87	Upstream gene	10p14	LOC105376400	1.35 (1.25-1.45)
rs11170164	T	0.09	missense	12q13.13	KRT5	1.29 (NR)

BCC, basal cell carcinoma; SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval; NR, not reported; 3′ UTR, three prime untranslated region.

[a] This table has been based on data available at www.ebi.ac.uk/gwas, accessed 20-02-2016 with the search term "basal cell carcinoma".[222]

[b] Mapped to dbSNP Build 146 and Genome Assembly GRCh38.p5.

PREVENTION

Primary prevention

The goal of primary prevention is to reduce the incidence of a first BCC. Even though UVR exposure is not solely responsible for the development of BCC, a considerable risk reduction is expected by adequate sun protection.[159] However, an Australian community-based RCT demonstrated that the daily application of sunscreen did not reduce the risk of BCC.[160] This finding could be partly explained by the occurrence of BCCs on sites that were not treated with sunscreen and the relatively high age of the included participants, and underlines the complex association between UVR and BCC.[160] Multiple national campaigns have been initiated to create public awareness, improve professional education and start behavioural change, such as the SunSmart programme in Australia.[161,162] Initially, these campaigns focused on informing people about the harmful effects of UVR exposure but now more actively try to influence behaviour. In addition, they target children and adolescents at schools, because minimizing (excessive) UVR exposure at an early age is a very important preventive measure.[161,163] At a legislative level, local governments were encouraged to adopt sun protection policies such as sales tax exemption for approved sunscreens and the creation of sufficient shade at schools and other public open spaces.[161,162] Commercial indoor tanning salons in Australia were banned completely as of 1 January 2015 and multiple other countries have restricted the use of indoor tanning as well.[164]

Although the awareness of the hazardous effects of excessive UVR exposure has increased over time, the incidence of most UVR-related skin cancers is still increasing, suggesting that people have not fully adopted this knowledge in their behavior (i.e., 'knowledge–behaviour gap'). Nevertheless, Australian studies reported the stabilization of NMSC rates for people younger than 60 years[10] and also showed a significant decline in excision rates for KCs in men and women younger than 45 years.[165] The positive effects of primary prevention programmes might become more evident over time, as the follow-up is still relatively short since the initiation of these programmes.

In addition to behavioural changes, the use of natural, synthetic or biological chemical agents to reverse, suppress or prevent carcinogenic progression to invasive cancer (i.e., chemoprevention) could be promising in reducing the BCC burden as well.[166] Chemoprevention could be used as both a primary and secondary prevention measure. Whether an agent is a good chemoprophylactic candidate is determined by the risk : benefit ratio. Many agents, such as beta carotene, selenium, synthetic retinoids (tretinoin, isotretinoin) and nonsteroidal anti-inflammatory drugs have been tested but showed no chemopreventive effect on BCC development.[160,167–172] However, when retinoids were used in patients with genodermatoses (NBCCS, XP) a more promising protective effect was seen on BCC development.[173–175] Another systemic

chemoprophylactic that works well in patients with NBCCS is the hedgehog pathway inhibitor vismodegib, but adverse events occur frequently.[176]

Secondary prevention

The goal of secondary prevention is to detect skin cancer at an early stage (screening) and to prevent metachronous skin cancers. Taking the Wilson and Jungner principles for population-based disease screening into consideration, BCC screening by itself is not likely to be cost-effective because the costs of case-finding (including diagnosis and treatment) are most likely in a nonacceptable relation to the overall healthcare costs.[177] In addition, the U.S. Preventive Services Task Force recently (2016) concluded that: 'the current evidence is insufficient to assess the balance of benefit and harms of screening for skin cancer in adults with a clinical visual skin examination'.[178] However, the German skin cancer screening programme showed that the skin cancer incidence went up during the screening period, but this does not necessarily mean that it was (cost) effective.[179]

A way of increasing the cost-effectiveness of screening is restricting screening to high-risk patients such as those with a history of BCCs. Recently, a prediction was developed that could reasonably assess the absolute risk of a second BCC using simple phenotypic, lifestyle and tumour-specific characteristics.[92] Further improving these prediction models in the coming years could help physicians identify these high-risk patients and give them the right follow-up. The downside of targeted screening approaches in high-risk patients is the so-called 'prevention paradox' in which you address the high-risk individual but not the overwhelming majority of low-risk patients that develop BCCs.[180]

Tertiary prevention

The goal of tertiary prevention is to soften the impact of (advanced/metastatic) BCC on patients' lives. A small group (about 1%) of patients have BCCs that have progressed to an inoperable stage or have metastasized, and these advanced BCCs were associated with a significant disease burden.[181,182] In order to improve their ability to function, their quality of life and their life expectancy, MMS, radiotherapy and vismodegib could be used.

IMPLICATIONS FOR HEALTH POLICIES

Overall impact

Although BCC-related mortality is low, both tumour growth and treatment can cause considerable functional and cosmetic morbidity. The recent U.S.A. initiative to rename

BCC to 'indolent lesion of epithelial origin (IDLE)' may be understandable from a public health perspective, but is inappropriate on an individual level because it falsely reassures patients.[183] In addition, the lay press recently minimized the consequences that BCC can have on the well-being of a patient, confirming the downgrading of BCC as a nonissue.[184] These controversial opinions could be a warning sign that policy-makers are developing a different view on BCC care.

Treatment-related impact

To provide the most appropriate BCC care, physicians should individualize the management of BCCs, taking tumour, patient and treatment characteristics into account, and combine this with patient preferences and needs (i.e., shared decision-making).[185] The dermatologist should be the lead of skin cancer management, but needs to combine diagnostic expertise with a high level of surgical skills to provide the optimal care. In addition to dermatologists, the general practitioner (GP) also can play an important role in BCC management. In countries such as Australia, where skin cancer poses a large burden on the healthcare systems, trained GPs with a special interest in skin cancer are functioning as specialized primary care physicians to detect and treat skin cancer. A Dutch study showed that the majority of GPs questioned were willing to extend their role in skin cancer care, including surgical excision of low-risk BCCs, but that they requested additional skin cancer training.[186]

Choosing the most cost-effective treatment for BCC wisely becomes increasingly important.[187] The positioning and appropriate use of MMS in the management strategy of BCC is crucial, because it drives the increment in costs related to BCC care.[35,188] Appropriate use of more costly treatments is warranted to ensure access to this more expensive treatment over the long term. Linos et al. have raised another controversial issue in BCC management among patients with limited life expectancy.[189] In a U.S.A. prospective cohort study, they showed that most NMSCs were treated surgically, regardless of the patient's life expectancy.[189] Although it remains a controversial topic, it should stimulate clinicians to provide individualized care in line with patients' needs, especially for certain subgroups of patients with BCC.

Follow-up-related impact

The underlying rationale to monitor patients with BCC is to identify recurrences and new tumours, educate and psychologically support and reassure patients.[190] This multidimensional rationale makes it difficult to generate consensus about frequency and duration of follow-up. For example, most clinical recurrences appear within 3 years, but up to 20% may occur within 5–10 years,[191,192] whereas the psychological stress often peaks in the first years after a cancer diagnosis.[193,194] In addition, the risk of metachronous BCCs is highest in the first 3 years after diagnosis, but remains elevated

over time.[115,195,196] The Dutch BCC guideline differentiates between high- and low-risk BCCs and recommends annual follow-up for high-risk BCCs.[197] In contrast, the U.K. guideline concludes, 'Clearly, within the British health care system it is not possible to offer long-term follow-up to all patients who have had their first and only primary BCC treated'.[198] Again, there is very little data to support both recommendations, but the costs of annual monitoring by dermatologists is a very expensive surveillance method because of the tumour's high incidence.

In contrast, there exists enough data that support that both the dermatologist and the GP should perform total body skin examinations in patients presenting with a primary BCC, because the chance of finding another synchronous BCC is significant.[115,199] Clinicians should also be aware of the increase in BCC incidence in younger (female) patients,[15] which could lead to an exponential increase in its occurrence in the future elderly population, because those with a history of BCC are likely to develop more of these tumours.[23]

A more cost-effective approach could be to invest in providing personalized information on BCC and its treatment, and educate patients on important risk factors, risks of metachronous skin cancer, sun avoidance measures, skin self-examination, and train GPs in after care of patients with skin cancer, but this needs to be studied in more detail as has been done for other cancers.

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SUPPORTING INFORMATION

Table S1. Main nongenetic risk factors for basal cell carcinoma (BCC), superficial BCC and multiple BCCs

	BCC	Superficial BCC	Multiple BCCs
Phenotypic factors			
Age	+ (higher)[1-8]	+ (lower)[9-12]	+ (higher)[13-22]
Sex[a]	+ (male)[4]	+ (female)[10,11]	+ (male)[13,17,19,20,23-26]
Light pigment status[b]	+[1-3,6-8,27-43]		
Low ability to tan (i.e., burn easily)	+[1-3,7,27,31,34-39,41,43-47]		
Painful/blistering sunburns	+[6,8,30,31,34,40,43,46,48]		
Childhood painful/blistering sunburns	+[28,29,35,36,38,39,49,50]		
Signs of actinic damage	+[3,4,6-8,28-31,33-35,38,41,44,45,51-53]		
Personal history of skin cancer	+[6,35,41]		+[13,21,54]
Family history of skin cancer	+[6,7,28,35,45,55,56]		
Truncal (first) BCC		+[9-12,57]	+[18,19,37,58,59]
Multiple BCCs at (initial) presentation			+[22,60]
Environmental factors			
Childhood intense intermittent UVR exposure	+[29,34,35,39,46,55,61]		
(Adult) intense intermittent UVR exposure	+[8,35,38-41,46,50,56,62]		
Indoor tanning	+[63-68]		
PUVA therapy	+[69-74]		+[75]
UVB therapy	+[71,73,76,77]		
Medical ionizing radiation	+[35,71,78-88]		+[84]
Non-medical ionizing radiation	+[89-92]		
Arsenic	+[93,94]		+[95]
Organ transplant recipients	+[96-100]		+[101]
Immunosuppressive agents	+[102-105]		

"+" means positively associated with the outcome and an empty cell means no (clear) association. References are shown in superscript. BCC, basal cell carcinoma; AK, actinic keratosis; PUVA, psoralen and ultraviolet-A; UVB, ultraviolet B.

[a] analyses were frequently adjusted for age and sex, but papers often don't report the effect sizes. However, from incidence studies it is clear that both age and sex are significantly associated with BCC.

[b] Consists of complexion, hair colour and eye colour.

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