The epidemiology of basal cell carcinoma

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Written and submitted by

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KEY WORDS

Basal cell carcinoma, Skin cancer, Prospective studies, Australia, Epidemiology, Keratinocyte cancer, Risk factors, Phenotype, Ultraviolet radiation, Solar elastosis
ABSTRACT

This PhD thesis represents development in the understanding of the epidemiology of the commonest skin cancer, basal cell carcinoma.

Basal cell carcinoma (BCC) is a skin cancer of particular importance to the Australian community. Its rate of occurrence is highest in Queensland, where 1% to 2% of people are newly affected annually. This is an order of magnitude higher than corresponding incidence estimates in European and North American populations. Individuals with a sun-sensitive complexion are particularly susceptible because sun exposure is the single most important causative agent, as shown by the anatomic distribution of BCC which is in general consistent with the levels of sun exposure across body sites. A distinguishing feature of BCC is the occurrence of multiple primary tumours within individuals, synchronously or over time, and their diagnosis and treatment costs contribute substantially to the major public health burden caused by BCC. A primary knowledge gap about BCC pathogenesis however was an understanding of the true frequency of multiple BCC occurrences and their body distribution, and why a proportion of people do develop more than one BCC in their life.

This research project sought to address this gap under an overarching research aim to better understand the detailed epidemiology of BCC with the ultimate goal of reducing the burden of this skin cancer through prevention. The particular aim was to document prospectively the rate of BCC occurrence and its associations with constitutional and environmental (solar) factors, all the while paying special attention to persons affected by more than one BCC. The study built on previous findings and recent developments in the field but set out to confirm and extend these and propose more adequate theories about the complex epidemiology of this cancer.

Addressing these goals required a new approach to researching basal cell carcinoma, due to the need to account for the phenomenon of multiple
incident BCCs per person. This was enabled by a 20 year community-based study of skin cancer in Australians that provided the methodological foundation for this thesis. Study participants were originally randomly selected in 1986 from the electoral register of all adult residents of the subtropical township of Nambour in Queensland, Australia. On various occasions during the study, participants were fully examined by dermatologists who documented cumulative photodamage as well as skin cancers. Participants completed standard questionnaires about skin cancer-related factors, and consented to have any diagnosed skin cancers notified to the investigators by regional pathology laboratories in Queensland. These methods allowed 100% ascertainment of histologically confirmed BCCs in this study population. 1339 participants had complete follow-up to the end of 2007. Statistical analyses in this thesis were carried out using SAS and SUDAAN statistical software packages. Modelling methods, including multivariate logistic regressions, allowed for repeated measures in terms of multiple BCCs per person. This innovative approach gave new findings on two levels, presented in five chapters as scientific papers:

1. Incidence of basal cell carcinoma multiplicity and detailed anatomic distribution: longitudinal study of an Australian population

   The incidence of people affected multiple times by BCC was 705 per 100,000 person years compared to an incidence rate of people singly affected of 935 per 100,000 person years. Among multiply and singly affected persons alike, site-specific BCC incidence rates were far highest on facial subsites, followed by upper limbs, trunk, and then lower limbs.

2. Melanocytic nevi and basal cell carcinoma: is there an association?

   BCC risk was significantly increased in those with forearm nevi (Odds Ratios (OR) 1.43, 95% Confidence Intervals (CI) 1.09-1.89) compared to people without forearm nevi, especially among those who spent their time mainly outdoors (OR 1.6, 95%CI 1.1-2.3) compared to those who spent their time mainly indoors. Nevi on the back were not associated with BCC.
3. Clinical signs of photodamage are associated with basal cell carcinoma multiplicity and site: a 16-year longitudinal study

Over a 16-year follow-up period, 58% of people affected by BCC developed more than one BCC. Among these people 60% developed BCCs across different anatomic sites. Participants with high numbers of solar keratoses, compared to people without solar keratoses, were most likely to experience the highest BCC counts overall (OR 3.3, 95%CI 1.4-13.5). Occurrences of BCC on the trunk (OR 3.3, 95%CI 1.4-7.6) and on the limbs (OR 3.7, 95%CI 2.0-7.0) were strongly associated with high numbers of solar keratoses on these sites.

4. Occurrence and determinants of basal cell carcinoma by histological subtype in an Australian community

Among 1202 BCCs, 77% had a single growth pattern and 23% were of mixed histological composition. Among all BCCs the nodular followed by the superficial growth patterns were commonest. Risk of nodular and superficial BCCs on the head was raised if 5 or more solar keratoses were present on the face (OR 1.8, 95%CI 1.2-2.7 and OR 4.5, 95%CI 2.1-9.7 respectively) and similarly on the trunk in the presence of multiple solar keratoses on the trunk (OR 4.2, 95%CI 1.5-11.9 and OR 2.2, 95%CI 1.1-4.4 respectively).

5. Basal cell carcinoma and measures of cumulative sun exposure: an Australian longitudinal community-based study

Dermal elastosis was more likely to be seen adjacent to head and neck BCCs than trunk BCCs (p=0.01). Severity of dermal elastosis increased on each site with increasing clinical signs of cutaneous sun damage on that site. BCCs that occurred without perilesional elastosis per se, were always found in an anatomic region with signs of photodamage.

This thesis thus has identified the magnitude of the burden of multiple BCCs. It does not support the view that people affected by more than one BCC represent a distinct group of people who are prone to BCCs on certain body
sites. The results also demonstrate that BCCs regardless of site, histology or order of occurrence are strongly associated with cumulative sun exposure causing photodamage to the skin, and hence challenge the view that BCCs occurring on body sites with typically low opportunities for sun exposure or of the superficial growth pattern are different in their association with the sun from those on typically sun-exposed sites, or nodular BCCs, respectively. Through dissemination in the scientific and medical literature, and to the community at large, these findings can ultimately assist in the primary and secondary prevention of BCC, perhaps especially in high-risk populations.
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ABBREVIATIONS

UV ultraviolet
UVR ultraviolet radiation
BCC basal cell carcinoma
SCC squamous cell carcinoma
UVA ultraviolet-A
UVB ultraviolet-B
UVC ultraviolet-C
KC keratinocyte cancer
NMSC non-melanoma skin cancer
XP xeroderma pigmentosum
95%CI 95% Confidence Interval
OR Odds Ratio
WHO World Health Organisation
% Percentage
pyar person years at risk
Statement of original authorship

The work contained in this thesis has not been previously submitted to meet requirements for an award at this or any other higher education institution. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made.

Signed ___________________________ Date __________________

Naomi Richmond-Sinclair, BApp Sci, Hons I

Candidate’s statement of contribution to Jointly-published work and Statement of contribution by others

The contributions of the candidate and the contributions of others to each included manuscript are described in detail preceding each manuscript in sections headed ‘acknowledgement of the contribution of the candidate and others’.

Statement by Principal Supervisor

All co-authors have provided their consent for the inclusion of the papers presented in this thesis and accept the candidate’s contribution to each manuscript as described in the statements of contribution of the candidate which precede each manuscript.

Signed ___________________________ Date __________________

Prof Adèle Green MBBC, MSc, PhD
PUBLICATIONS

Publications by the Candidate Which Form Part of the Thesis


2. Richmond-Sinclair NM, van der Pols JC, Green AC. Melanocytic nevi and basal cell carcinoma: is there an association? This manuscript will soon be submitted to an international peer-reviewed journal.


4. Richmond-Sinclair NM, van der Pols JC, Muller HK, Green AC. Occurrence and determinants of basal cell carcinoma by histological subtype in an Australian cohort. This manuscript will soon be submitted to an international peer-reviewed journal.


Publications by the Candidate Relevant to the Thesis but not Forming Part of it (see Appendix 1)


Refereed Conference Papers

Material arising from this thesis has previously been presented by the Candidate at the following conferences


Doctoral colloquia

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CHAPTER 1

Review of literature and research questions
1.1 Introduction

Basal cell carcinoma (BCC) is the most common human malignancy and among Caucasian populations it is the predominant cancer of the skin (Zedan et al.) (All references from Chapter 1 can be found in the final List of References). The highest reported incidence rates are recorded for Queensland, Australia where 1 to 2 people per 100 are affected annually (Raasch and Buettner, 2002). This is an order of magnitude higher than corresponding estimates in European and North American populations. Sun exposure is the single most important causative agent, and the anatomic distribution of BCC is in general consistent with the levels of sun exposure across body sites (Diffey et al., 1979). A distinguishing feature of BCC is the common occurrence of multiple primary tumors within individuals, synchronously or over time, and it is their treatment costs that underscore the major public health relevance of BCC (Joseph et al., 2001; Mathers et al., 1999).

This literature review has a dual purpose. First, it will provide an overview of pertinent areas of research in order to position this study within its field. There is an extensive focus on the frequency of this disease and the causal and susceptibility factors of this skin cancer. Thus this body of work centres on the epidemiology of BCC. Secondly, this literature review is a collection of evidence that supports the identification of gaps in the field and thus establishes its potential significance and its innovative contribution to knowledge. The literature search that forms the basis of this literature review was performed largely in Entrez Pubmed (http://www.ncbi.nlm.nih.gov/sites/entrez), which was accessed regularly throughout the duration of the research. In order to place BCC within the context of human body anatomy, exposures, and other pathological skin conditions a vast array of literature was read and integrated into the literature review. However, its scope was limited to concentrate on prominent research and the latest publications within each area. Papers were selected to offer a balanced representation of both Australian and international research.
Basal cell carcinomas are not routinely recorded at cancer registries, thus incidence estimates in northern and southern hemisphere populations have largely come from *ad hoc* studies (these studies are further discussed in 1.4.1 Rate of Occurrence below). This is also true for many studies that have sought to identify risk factors for BCC (these studies are further discussed below in 1.4.3 Risk Factors). Cellular- and molecular-based investigations often rely on ex vivo and animal model experiments to advance the understanding of BCC pathogenesis in relation to phenotype and environmental exposures but rarely translate the results adequately into human in-vivo knowledge. This research project seeks to in-part address these gaps, based on a unique resource, namely the Nambour Skin Cancer Study.

1.2 Skin structure and function

In its normal capacity, human skin is the natural boundary between the person and their external environment. Skin belongs to the integumentary system and in terms of body weight, is the largest human organ (Goldsmith, 1990). Skin originates from the juxtaposition of the embryological ectoderm and underlying mesoderm, which give rise to the epidermis and the dermis respectively. It is highly differentiated and dynamic; responsible for a range of precise functions. The two main types of skin are non-hairy, found on the soles and palms, and hair-bearing skin. Functions include homeostatic support through regulation of body temperature, protection from pathogens and mechanical and chemical insults, sensory reception and pigmentation. Whilst the skin layers appear independent of one another, they do cooperate to perform these skin-specific functions. As the body’s outermost layer skin is susceptible to damage from external influences.
1.2.1 Epidermis

The stratified, multi-cellular epidermis is a continually renewing epithelium. It has four levels of differentiation based on keratinocyte morphology (see Keratinocytes section below and Figure 1.1) (Freinkel and Woodley, 2001; Rook, 2004). As the most superficial layer, the stratum corneum is the barrier to water loss (containing 15-30 sheets of flattened terminally differentiated keratinocytes called corneocytes). The concentrated keratin within these cells is also the primary obstruction between ultraviolet radiation (UVR) and epidermal DNA. The next, inner, layer is composed of 3-5 sheets of non-dividing keratinocytes that produce cytoplasmic basophilic keratohyalin granules (Holbrook, 1989). Immediately below are 8-10 sheets of keratinocytes with limited ability for cell division that produce spinous-shaped
keratinocytes. The innermost layer, the basal layer, contains columnar-shaped, mitotically active keratinocytes and keratinocytes with stem cell-like properties. It is here, that immigrant cells such as melanocytes, Langerhans and Merkel cells can enter the epidermis. Blood vessels do not infiltrate the epidermis; it receives nourishment by diffusion from the dermis. Cells within the basal layer are anchored to a non-cellular basement membrane that is the division between the epidermis and dermis.

**Keratinocytes**

Keratinocytes are the major cell type of the epidermis. They originate in the basal layer from the mitotic division of keratinocyte stem cells and their transient amplifying daughter cells. A proportion of the dividing basal keratinocytes are stem cells (Watt, 2001), and they reside in clusters in the interfollicular basal epidermis and in the bulge region of hair follicle. As these cells differentiate and travel through the epidermal layers they accumulate quantities of the protein keratin, which acts as a structural matrix, until they apoptose and are completely keratinised. At the end of this process, which takes about a month, they are shed and replaced. Each layer is composed of a different amount of keratin, ranging from approximately 30% in the basal layer up to 80% in the stratum corneum (Tobin, 2006).

**Melanocytes**

Embryologically, melanocytes arise from the neural crest and reside in the basal layer of the adult epidermis (Erickson, 1993; Weston, 1970). The number of these pigment synthesising cells is constant across individuals (Szabo, 1959). However, the level of melanin-production and distribution
varies; yielding skin colour variation. The melanin protein is produced in the melanosome, a specialised and melanocyte-specific organelle (Freinkel and Woodley, 2001). This biochemical process is continuous and is termed melanogenesis (Slominski et al., 2004). Production is regulated and heavily influenced by UVR exposure. Melanosomes are transferred to the keratinocytes where they sit atop the nucleus, lessening the amount of UVR reaching the cells’ DNA. Two types of cutaneous melanin have been described: eumelanin and pheomelanin (Rook, 2004). The former produces brown-black colours; the latter provides yellow-red colours and is more prominent in fair-skinned individuals (Rook, 2004).

1.2.2 Dermis

The epidermis and dermis are detached from one another by the dermal-epidermal junction, to which they are both anchored. The major constituent of this is the basement membrane serving as the interface and filter (Freinkel and Woodley, 2001). Of mesodermal origin, the dermis acts as a structural support and nutrient-provider for the cells of the epidermis. Regional variation based on the size of collagen fibrils and cell density, splits the dermis into two layers. The upper papillary dermis interweaves with the epidermis, is cell-rich and here the collagen fibrils are smaller in diameter compared to those of the deeper reticular dermis which blends with subcutaneous fat tissue. The principal cellular elements are fibroblasts, responsible for the manufacture of dermal connective tissue elements or their precursors, and mast cells, which have a significant role in the event of an allergic reaction. The dermis contains blood vessels and lymphatic capillaries that provide nourishment to the basal layer of the epidermis. It is also filled with sensory and motor nerve endings and is abundantly supported with secretory and excretory glands, namely eccrine, apocrine, apoeccrine and sebaceous glands, and hair follicles (Freinkel and Woodley, 2001).
Hair

Hair is characteristic to the mammalian class and the human body is almost entirely covered by millions of highly structured hair follicles (Dawber, 1997; Paus and Peker, 2003). In humans, hair has little purpose except for the protective capabilities of eyebrows, eyelashes, nose and ear hair, and physical differentiation within society. In the adult two hair types are recognised: vellus and terminal. Vellus hairs found on most body sites are short (< 1 cm), light coloured and thin. Terminal hair is the thicker and darker hair of the scalp, and is more widespread on males (Rook, 2004).

Hair follicle structure

Hair follicles are the structures that produce hair, and similar to cutaneous keratinocytes they are constantly renewed, undergoing continual cycles of growth and regression. Embedded within the dermis, hair follicles are distributed in a periodic pattern. It is believed that few, if any hair follicles are formed after birth and that their density reduces with advancing age (Giacometti, 1965). Between races, the vellus and terminal hair follicle density (number of hair follicles per unit area) varies but the chemical composition of hair protein is uniform (Lee et al., 2002; Loussouarn, 2001; Mangelsdorf et al., 2006; Sperling, 1999; Whiting, 1993). However, within any one ethnic group, these measures are similar among individuals, with density varying dramatically according to body site, and the highest being consistently recorded on the facial region (Blume et al., 1991; Otberg et al., 2004).

Structurally, hair follicles lie at an angle to the skin surface. Two distinct layers line the length of the hair follicle: the keratin rich outer and the inner root sheaths. The former extends the follicle’s entire length whilst the latter stops in line with the sebaceous gland and has some contact with the hair shaft. Giving rise to these inner and outer layers of the hair fibre are germinative cells. They have a high division rate and surround the papilla.
located at the base of the hair follicle. On one side of the follicle, within the outer root sheath is the bulge region. Anatomically, this appears as a thickened region and functionally, it harbours stem cells (Akiyama et al., 1995; Lyle et al., 1998). The continual regeneration of the hair follicles relies upon these stem cells. Attached to the bulge are the erector pili, a bundle of smooth muscles, which enable the hair to stand vertically when contracted. Further up the hair follicle, is the sebaceous gland whose gland size, density and activity vary depending upon the local milieu of the body site (hormones) (Randall et al., 2000). Only on mucosal membranes are sebaceous glands found in absence of hair follicles (for example, the lips). They are found in high density on the scalp and face, at up to 200 sebaceous glands cm\(^{-2}\), and not at all on the palms, soles and dorsum of the feet (Tobin, 2006). The primary function of sebaceous glands is the production of sebum, a yellowish viscous fluid that mainly contains lipids (Tobin, 2006). These glands are also involved in steroidogenesis and possibly the production of anti- and pro-inflammatory compounds (Zouboulis, 2004). A hair follicle together with its sebaceous gland is traditionally termed ‘the pilosebaceous unit’.

1.3 Clinical and pathological diagnosis

1.3.1 Clinical diagnosis

With regard to sun-induced lesions, the appearance of BCC is generally distinct clinically (Rook, 2004). Basal cell carcinoma may develop anywhere on the skin surface and whilst the majority of these cancers are slow growing in nature and confined to the anatomic sub-site of origin they can be very destructive to the local anatomy (Rigel, 2005). Patients may acquire new primary BCCs more than once (synchronously and metachronously). Recurrent BCCs, on the other hand, present at the sites of previously treated BCCs.

The appearance of BCC may vary for several fundamental reasons including stage at diagnosis and histological type. Early tumours appear small,
translucent, raised and rounded and dilated superficial blood vessels may infiltrate (Rook, 2004). With disease progression the lesions tend to maintain their original growth pattern extending peripherally in a slow and locally invasive manner (Telfer et al., 1999). A common type is the *Nodular* BCC; typically raised, shiny and pearly with defined margins (Rigel, 2005). The degree of vascularity varies and ulceration occurs late in development. *Superficial* types tend to be bright pink and shiny in appearance, but are less well-defined erythematous macular lesions (Rigel, 2005); vascularity and pigmentation may be present. The *Morphoeic* BCC looks like a pale scar and patients can be unaware of them. They have a disposition to be deeply invasive, due to a sclerosing growth pattern with fibrosis causing greater tissue destruction (Rook, 2004). Mixed types occur also, making diagnosis difficult.

The clinical diagnosis of BCC is not without difficulty but accurate diagnosis is important, especially in high risk populations. In the primary care setting the initial diagnosis is normally made by a general practitioner or dermatologist and a suspected clinical diagnosis is often verified histologically (Streeton et al., 2006). A recent Australian-based study compared the clinical and histological diagnosis of excised skin lesions in 8694 patients; they reported that clinical diagnostic accuracy was highest for BCC (positive predictive value (PPV) 72%) when compared with squamous cell carcinoma and melanoma (PPV 49% and 33% respectively) (Heal et al., 2008). Similarly, Youl et al. compared the diagnostic accuracy of skin lesions among general practitioners and doctors within primary care “skin cancer clinics”. They reported that the overall clinical accuracy for diagnosing skin cancer was similar between general practitioners and skin cancer clinic doctors, and the latter group had greater sensitivity when diagnosing BCC and melanoma (Youl et al., 2007).
1.3.2 Histology

In 1827 the first description of BCC was recorded by Sir Arthur Jacob (1790-1874) (Jacob, 1827). Jacob’s account encompassed the well-defined margins of BCCs, their lack of potential to metastasise and the limited morbidity of those affected (Jacob, 1827). Edmund Krompecher later differentiated BCC from other epithelial tumors and suggested they are derived from the pluripotent, undifferentiated cells of the basal layer of the epidermis or the cutaneous appendages (Krompecher, 1903).

On this basis it is not surprising that at least twenty histological subtypes have been described subsequently (Slater, 2002), among them several common growth patterns ((NHMRC), 2002). Histological classification is traditionally based on the extent and type of differentiation with acknowledgment of the growth pattern. Typically, tumour cells resemble those of the basal layer of the epidermis and the matrix cells of the appendages. They are noted for their compact nuclei, small cytoplasm and interaction with the adjacent dermis which produces their well organised stroma (Freinkel and Woodley, 2001). The interaction with the dermis, a principal function of the normal basal cell, produces the characteristic marginal palisade of tumour cells. Some lesions may have a degree of differentiation toward epithelial adnexa but in most cases this is not true to the derivation of any individual epithelial structure. Histological differentiation may occur because, during development, tumour cells may sever their connection to epithelial appendages or establish a secondary connection to structures to which it becomes close. Of the common types, the superficial and morphoeic variants each have a representative histopathologic image that differs slightly from lesion to lesion. The most common subtype Nodular, which accounts for up to 80% (Boi et al., 2003) can show many different histopathological variants.

To provide examples of typical histological pictures of the common variants: superficial BCCs show horizontally arranged lobules of atypical basal cells in the papillary dermis that maintain epidermal contact yet there is minimal
extension into the lower epidermis. The *morphoeic* type has fine radiating extensions that complicate margin identification and show no residual association with the epidermis and epithelial structures. *Nodular* BCCs are characteristically dome-shaped, composed of irregularly sized and shaped islands of basaloid cells with a circumscribed growth pattern.

1.3.3 Cell of origin theories

When compared histologically to other cutaneous lesions, BCCs show little cellular organisation. Research has propagated many theories about the cell of origin of this common cancer. Among them are the basal cells of the epidermis, the infundibular and the outer root sheath of the hair follicle, dormant primordial epithelial germ cells, cells of the pilosebaceous unit and cells of appendageal structures other than the hair follicle (Lang and Maize Sr, 2005). Pioneering studies using light microscopy to detect the earliest signs of proliferation in human tumours and experimental tumours of the rat pointed to the outer root sheath of the hair follicle and the interfollicular epidermis as the site of origin (Miller, 1991; Zackheim, 1962, 1963). At this cellular position, it is possible for the tumour to grow with the epidermis, however, recent investigations point to the epidermal stem cell populations that reside in the hair follicle bulge and in a non-random distribution within the basal cells of the interfollicular epidermis (also termed keratinocyte stem cells). At the present pluripotent germinative cells of the epidermis and bulge region of the hair follicle are considered a likely cell of origin allowing the BCC to develop into any of the epithelial structures (Barthel and Aberdam, 2005; Tilli *et al.*, 2005).

1.4 Epidemiology

1.4.1 Rates of occurrence

*Validity of reported estimates*
In most countries it is not a legal requirement of the treating doctor to notify population-based cancer registries of keratinocyte cancer. In some countries, notification is optional, leading to incomplete data. This is for various reasons, depending on the country: the ubiquity of the lesions and resulting logistical difficulties in sustaining correct records (high incidence) or the lack of severity (low incidence) (Green and Maclellan, 1989). Furthermore, a portion of BCCs are treated without surgical measures and not histologically confirmed (Albert and Weinstock, 2003; Streeton et al., 2006). Consequently incidence estimates in northern and southern hemisphere populations have largely come from ad hoc studies (these studies are further discussed in 1.4.1 Rate of Occurrence below). It is therefore likely that the BCC estimates that are available are in fact underestimates of the true rate of occurrence, hence accurate and representative epidemiological findings of BCC are sparse.

1.4.1.1 Incidence

BCC is the commonest cancer in Caucasian populations worldwide (Telfer et al., 1999) (Bower et al., 2000; Diepgen and Mahler, 2002).

Australia

A survey in 2002 of over 57,000 Australians estimated an age-standardised incidence rate of 884 BCCs per 100,000 persons (Staples et al., 2006). Findings from the same investigation showed that incidence increased with age and was generally higher in men than women in each age group. Incidence peaked at ages 70 years or older at 5308 BCCs per 100,000 persons: 7051 and 3880 BCCs per 100,000 men and women respectively. Incidence (Staples et al., 2006). The same National survey data indicated the incidence of BCC had increased by 35% in 18-years leading up to 2002 (Staples et al., 2006). Despite the high incidence rates of BCC, the case
fatality rate is low at 2.0 per 100,000 for males and 0.6 per 100,000 for females (AIHW, 2004).

Repeated occurrences

Basal cell carcinoma has a predilection to occur more than once, either synchronously or over time, in a proportion of people affected. Since no previous estimates however have accounted for this occurrence of multiple BCCs per person, these previous studies would have underestimated the true BCC tumour incidence.

Australian national survey data for the year of 2002 revealed that 27% of people affected by BCC (where 81% were histologically confirmed) experienced more than one BCC. This proportion was similar for males and females (Staples et al., 2006). In a tropical Australian community, over a 3-year period, 26% of people affected by BCC were treated for more than one BCC (Raasch and Buettner, 2002). It was not made clear in either of these studies whether peoples’ BCCs were diagnosed at the same or different times. When describing the occurrence of multiple BCCs within the Nambour Skin Cancer Trial, Pandeya et al. found that 47% of people who had developed a BCC experienced a second primary BCC, and of these 50% went on to develop a third primary BCC, all within a 4.5-year period (Pandeya et al., 2005). In the Australian population the incidence of people affected by multiple BCCs has not been estimated previously.

International

Selected incidence estimates for countries other than Australia are presented in order of decreasing latitude (of the major city in the respective region). They are presented separately because incidence estimates for different geographical regions have been age standardised to different populations and are therefore not directly comparable.
The Netherlands (Latitude 52°N)
Using cancer registry data it is estimated that 93 males and 82 females were affected by BCC per 100,000 person-years at risk (pyar) in the Netherlands from 1973 to 2000 (European age standardised) (de Vries et al., 2004). Incidence rates increased with advancing age in both sexes, but in particular among young women. In the same population, for the period 1973 to 2000 the estimated annual percentage increase in BCC incidence for males and females was 2.4% and 3.9% respectively (de Vries et al., 2004).

United Kingdom (Latitude 51°N)
Recent estimates from the United Kingdom indicate BCC affected 60 persons per 100,000 pyar in 1996 to 2003 (world age standardised) (Bath-Hextall et al., 2007a). The incidence of BCC was slightly higher among men than women: 69 and 53 persons per 100,000 pyar, respectively. During the period, 1996 to 2003, there was a 3% increase year by year and this trend was strongest for those aged 30 to 39 years (Bath-Hextall et al., 2007a).

North America (Latitude 30-47°N)
A cross-sectional study in 1993-1994 of the state of New Hampshire (latitude 43°N), indicated BCC occurs at a rate of 310 and 166 per 100,000 persons for males and females, respectively and increased with age (these estimates are general and inclusive of all ethnic groups, and age standardised to North America) (Karagas et al., 1999). When the latter estimates are compared to the corresponding estimates for 14 years earlier there was an annual 4% increase for both men and women (Karagas et al., 1999). In the southeast of Arizona (latitude 33°N) the incidence of BCC in 1996 was 936 and 497 per 100,000 persons for male and females respectively (these estimates are general and inclusive of all ethnic groups) (Harris et al., 2001). Over the period 1985 to 1996 there was an increase in the incidence of BCC, however, this was not a steady increase with some years showing a reduced incidence compared to the previous year.

Singapore (Latitude 1°N)
The most recently reported incidence rate of BCC in Singapore was 5.5 per 100 000 pyar during 1993 to 1997 (Koh et al., 2003). The incidence among males and females was similar. According to ethnic groups, the Chinese people had the highest BCC rates (6.4 per 100 000 pyar among males), followed by the Malays (3 per 100 000 pyar among females) and then Indians (1.4 per 100 000 pyar among females).

The overall incidence of BCC increased significantly during 1968 to 1997 with an annual increase of 3%.

Repeated occurrences

In northern hemisphere populations in temperate climates, where the incidence of single BCC does not reach 1% (Bath-Hextall et al., 2007a; Karagas et al., 1999), multiplicity of this skin cancer is still observed (Lear et al., 1997; Levi et al., 2006). A study using Swiss cancer registry data revealed the risk for second BCC was higher among people who were diagnosed with their first BCC at a young age (Levi et al., 2006). Furthermore, the cumulative incidence of a second BCC increased with time since diagnosis of the first BCC: 11% at 5-years, 21% at 10-years and 40% at 20-years. This finding was further supported by a meta-analysis of seven separate studies previously conducted on American populations: following a first BCC the incidence of subsequent BCC increased by a factor of 10, compared to those not affected by BCC and with no known genetic susceptibility (Marcil and Stern, 2000).

Incidence and repeated occurrences overall

In general as above, international estimates for the incidence of BCC are less than the corresponding estimates from Australian populations. This is because the Australian population are predominantly Caucasian and live in closer proximity to the equator than those living in the northern hemisphere. Regardless of geographic region, BCC incidence estimates increase with advancing age and are almost always higher for men than women.
Furthermore the incidence of this skin cancer appears to be increasing with time and it is likely there is a combination of reasons behind this, including, increased outdoor activities, change in clothing habits, increased longevity, ozone depletion all of which reflect a greater opportunity for sun-exposure, and as a result of skin cancer awareness and prevention campaigns more people present for treatment (Diepgen and Mahler, 2002; Gloster and Brodland, 1996)

1.4.2 Anatomic distribution

Like other sun-induced cutaneous cancers, BCC occurs frequently on anatomical sites exposed to solar UVR.

Australia

The anatomic distribution of BCC is generally well described for the Australian population. Information is needed however, on the specific anatomic subsites affected by BCC. The results of the 2002 keratinocytic skin cancer survey of 57,215 people (Staples et al., 2006), of whom 817 had a BCC in the previous 12 months, revealed that the head and neck region followed by the trunk had the greatest relative tumour density (calculated as the ratio of the proportion of tumours at a particular site to the proportion of total skin surface area of that site). In a prospective population-based survey in tropical north Queensland, including 2,327 patients with 3,538 BCCs, by far the most BCCs were excised from the face (males: 43%, females: 51%) followed by the posterior trunk (males: 15%, females: 9%) (Buettner and Raasch, 1998). The same study also reported site-specific incidence rates of BCC that were extreme on the ear, nose and cheek for men (56,402 per 100,000 body units) and women (29,879 per 100,000 body units) (Buettner and Raasch, 1998). In men, the neck, posterior trunk and shoulders and in women the neck, shoulders and arms also showed extreme incidence rates of BCC. These findings reflect the results of an earlier skin cancer survey of
tropical north Queensland (Raasch et al., 1998). Among each of these studies, the hands and feet were rarely affected by BCC.

**Histological subtypes**

One Queensland-based study to report the anatomic distribution of BCC by histological subtype revealed that the nodular, infiltrative and micronodular BCC were most common on the face for both sexes, while superficial BCCs were most frequent on the posterior trunk among males and the upper limbs among females (Raasch et al., 2006). A Victorian study of 3885 BCC patients reported that the nodular growth pattern was the most common overall (64%) and at each subsite, especially the head and neck where it accounted for 65% of specimens taken from this site (McCormack et al., 1997). Superficial BCCs accounted for 15% of BCCs overall and they were roughly equally distributed between the trunk, lower limbs and upper limbs (29%, 27% and 23% respectively) (McCormack et al., 1997).

**Repeated occurrences**

The anatomic distribution of BCCs among people affected by more than one BCC has not previously been described within the Australian population. It is not known if overall site distribution varies between people with a single BCC and those with multiple BCC occurrences or between males and females.

**International**

Retrospective studies originating in the northern hemisphere report that BCCs of the head and neck region account for at least 69% of lesions (Bastiaens et al., 1998; Diepgen and Mahler, 2002; Scrivener et al., 2002). The next most common site is the trunk (posterior and anterior trunk are grouped together), hosting 12% to 21% of tumours (Bastiaens et al., 1998; Scrivener et al., 2002). These findings were supported by an Italian case-control study (Pelucchi et al., 2007) and further corroborated by two reports.
from population-based cancer registries in Switzerland and the USA (Franceschi et al., 1996; Harris et al., 2001). Using the Swiss population-based cancer registry data, Franchesci et al reported that that highest rate of BCC (per unit surface area) were seen for both males and females on the face, followed by the neck, ears and scalp and the trunk (Franceschi et al., 1996).

Few studies have considered anatomic subsite distribution of BCC: Pearl and Scott, using combined data from five datasets, reported an excess of BCC on the nose (Pearl and Scott, 1986). BCCs were more common on the ears among males than females but the reverse was true for the lower leg (Pearl and Scott, 1986). Lovatt et al found truncal BCC to be significantly more common in males (Lovatt et al., 2004).

**Histological subtypes**

In a large retrospective study of BCC in France with some 10 245 people affected by BCC, both the nodular and morpheic BCCs were predominant on the head (90% and 95% respectively), whereas superficial BCCs most commonly occurred on the trunk (46%) (Scrivener et al., 2002). The predominance of the nodular type for the head and neck, and the superficial subtype for the trunk was also observed in a retrospective collection of 1711 Dutch people and their BCCs and an Italian case-control study (Bastiaens et al., 1998; Pelucchi et al., 2007). No studies have assessed the proportion of BCC histological subtypes according to anatomic subsite.

**Repeated occurrences**

One study described, in broad terms that people with multiple BCCs tend to develop their BCCs on a single site (Ramachandran et al., 2001), however, there was no explicit evidence provided about the proportion of people who developed BCC on a single anatomic site or on more than one anatomic site. In contrast, a hospital-based study in the Netherlands with a median follow-up time of 3.1-years revealed that 33% of people affected by multiple BCCs
were affected across different sites (van Iersel et al., 2005). Furthermore in an American study 45% of people affected by multiple BCCs developed BCCs on different anatomic sites during 7-years of follow-up (Marghoob et al., 1993).

1.4.3 Risk Factors

BCC pathogenesis occurs as a result of a complex of factors both endogenous and exogenous to the human body. These include: solar ultraviolet radiation, constitutional factors, arsenic, ionising radiation and immunosuppressive treatments. The following paragraphs acknowledge those risk factors for which the majority of BCCs are likely attributable to (solar ultraviolet radiation and constitutional factors).

1.4.3.1 Solar ultraviolet radiation

Ultraviolet radiation (UVR) is the component of the sun’s rays that cannot be seen or felt but has the preeminent role in skin cancer causation. There are three main components to UVR, namely UVA\(_{320-400\,\text{nm}}\), UVB\(_{280-320\,\text{nm}}\) and UVC\(_{200-280\,\text{nm}}\) (Green and Whiteman, 2006). The latter is entirely blocked by the ozone layer leaving only UVA and UVB to reach the Earth’s surface. The quality and quantity of UVR is determined by many factors. The time of day and season have a direct role in the amount of UVR that reaches the Earth’s surface such that up to 30% of the total UVR is received between 11am and 1pm especially during Summer months (Mattts, 2006). On a global scale factors that increase the UVR at the Earth’s surface include decreasing latitude, increasing altitude and cloud cover (Mattts, 2006). All UVR that reaches the skin’s surface has potential carcinogenic effects and the principal mechanism of action is via DNA damage where UVB acts directly and UVA indirectly. UVB produces dimers, which interrupt the functionality of the DNA. They usually take on the form of C to T or CC to TT mutations at
dipyrimidine sites and are typically called ‘UV signatures’. UVA causes the production of reactive oxygen species within cells (Halliday, 2005). Whilst skin cells have mechanisms in place that lessen these photo-biological products through the repair of DNA and mopping up of reactive oxygen species (Ravanat et al., 2001) this does not always happen efficiently and carcinogenesis is a major consequence.

Solar ultraviolet radiation and basal cell carcinoma

Sun exposure is considered the major environmental factor that causes BCC pathogenesis (Rubin et al., 2005). Its association with BCC development is traditionally supported by a strong inverse latitudinal gradient (Muir et al., 1987) and distribution that is consistent with general levels of sun exposure across body sites (International Agency for Research on Cancer, 1992).

Although evidence is available for an association between general BCC occurrence and cutaneous sun damage, it is not known how acute and chronic sun damage interrelate in BCC pathogenesis. In previous analytical epidemiological studies, BCC’s association with sun exposure has been supported by various degrees of evidence. In order of increasing objectivity measures of solar exposure that have been used include self-recalled sun exposure, clinical, and histological evidence of photodamage.

The effects of the UV bands in epidemiological studies are difficult to separate, and UVR exposure usually refers to the effects of both UVA and UVB. Within the cause and effect model (UVR and BCC) the carcinogenic effect of UVR is not fully understood, but the various cutaneous effects of sun exposure as known are discussed below in relation to BCC.

Self-recalled sunburns

Sunburns are a consequence of acute overexposure to UVR for the skin type concerned and they are associated with BCC. With regard to self-reported acute sun exposure six independent studies have shown that self-reported
histories of sunburns are strongly associated with BCC risk (Green et al., 1996; Kricker et al., 1991; Naldi et al., 2000; van Dam et al., 1999; Walther et al., 2004; Zanetti et al., 1996). Previous findings from the Australia community-based Nambour study found the odds for BCC to be almost 2-fold higher among people with a history of six or more sunburns compared to people with no sunburn history (Green et al., 1996). In the Health Professionals Follow-up Study a history of any number of sunburns increased the risk for BCC significantly (van Dam et al., 1999). In an Italian case-control study, two or more sunburns under the age of 15 years was associated with a 4-fold increase in the odds for BCC compared to people with no sunburns before age 15 (Naldi et al., 2000). A study that recorded information about sunburns at specific anatomic sites found a significant association with painful sunburns at the site of BCC occurrence (Kricker et al., 1991).

Although numerous epidemiological studies support a significant association between sunburn history and BCC development, sunburn history is a particularly subjective measure of sun damage. There is mixed literature surrounding the reliability of sunburn recall among adults (Berwick and Chen, 1995; Shoveller and Lovato, 2001; van der Mei et al., 2006) and naturally no study has been able to truly document the accuracy of sunburn recall during individuals’ lifetimes. Consequently it is difficult to assess the true association between acute intense patterns of sun exposure and BCC.

**Self-recalled recreational and occupational activities**

Studies that have investigated BCC’s association with cumulative sun exposure, by recall of outdoor occupational and recreational histories, consistently have reported weak or even negative associations (Gallagher et al., 1995; Green et al., 1996; Rosso et al., 1996). In a small Canadian case-control study those with self-reported high occupational sun exposure did not have increased odds for BCC (OR=1.4, 95%CI 0.8-2.4) compared to people with the lowest mean occupational exposure (Gallagher et al., 1995). In the same study, people with the highest value of mean recreational sun exposure
per year during their lifetime had negative odds for BCC (OR=0.4, 95%CI 0.2-1.0) when compared to people in the lowest category of exposure. However, with regard to recreational sun exposure under the age of 20 years, those with the highest mean value per year did have increased odds for developing BCC (OR=2.6, 95%CI 1.1-6.5). A larger European case-control study also found that people with a high lifetime number of outdoor work hours did not have increased odds for BCC (OR=1.0, 95%CI 0.8-1.3) compared to those in the lowest category of lifetime outdoor work hours (Rosso et al., 1996); they did however, find that people with a high number of hours spent at the beach during holidays were significantly more likely to be affected by BCC (OR=1.5, 95%CI 1.2-1.8). Furthermore, an Italian case-control study that found no association between summer holidays at the beach after age 20 and BCC development, did find that the longer a person spent at the beach during summer holidays under the age of 20 increased their odds for BCC significantly (Corona et al., 2001). In the Australian Nambour study neither people with mainly outdoor occupations or recreational activities had increased odds for developing BCC (OR=1.4, 95%CI 0.8-2.3 and OR=1.3, 95%CI 0.7-2.5 respectively) compared to people who spent their time mainly indoors (Green et al., 1996). These findings may be explained in part by the self-selection of people with fair or medium complexions and a tendency to burn to not have outdoor long-term occupations in Queensland even though they represented over 80% of the community study sample (Green et al., 1996).

All in all, there is some variation in the reported associations between occupational and recreational exposure and BCC development. Some findings suggest that irregular rather than chronic sun exposure is more strongly associated with BCC development. The findings do suggest, however that sun exposure early in life, in particular through recreational activities, is more important than regular sun exposure later in life.
Chronic photodamage occurs as a response to long-term overexposure to UVR (Evridiki et al., 2006). It is increasingly common with increasing age on exposed body sites among white skinned populations. Typical clinical markers of photodamage include telangiectasia (small dilated blood vessels near the surface of the skin), clinical elastosis (yellow discolouration and thickened and lined skin surface), solar lentigines (flat, pigmented and irregularly shaped benign lesions) and solar keratoses (thickened scaly growth of mature keratinocytes) (Yaar and Gilchrest, 2007). It should be noted that evidence for the association between overexposure to UVR and photodamage usually does not elucidate the exact pattern and dose of UVR, an inherent problem to the study of UVR. Photodamage is usually measured clinically and is therefore a more objective measure of past long-term sun exposure than recalled sun exposure.

Focussing on solar keratoses, several independent studies (one cohort, four case-control) have quantified the significant value of these as a risk factor for BCC (Corona et al., 2001; Green et al., 1996; Kricker et al., 1991; Naldi et al., 2000; Walther et al., 2004). Two Italian case-control studies reported the presence of solar keratoses increased a person’s odds for BCC about 3-fold (Corona et al., 2001; Naldi et al., 2000), whereas a German case-control study found the presence of solar keratoses increased the odds for BCC development over 7-fold (Walther et al., 2004). One Australian case-control study found an increasing number of solar keratoses was associated with increasing odds for BCC, such that 40 or more solar keratoses increased a person’s odds for BCC development over 10-fold when compared to people without these skin changes (Kricker et al., 1991). The only cohort study to assess the predictive value of solar keratoses to date has been the Nambour community-based study that found the risk for BCC was 2.5 times higher among people with up to 10 solar keratoses and 4 times higher among people with 11 or more solar keratoses when compared to people without solar keratoses (Green et al., 1996).
Photodamage is a robust determinant of BCC development, however previous studies have assessed the total body solar keratosis counts and thus it is not known if there is a specific association between solar keratoses and BCC site of occurrence. Photodamage has not been investigated in relation to multiple BCCs.

**Histological markers of photodamage**

At the objective tissue level, two previous studies have measured the degree of solar elastosis histologically in and around BCC tumour tissue (Zaynoun et al., 1985) or in adjacent normal skin (Kaur et al., 2006; Moon and Oh, 2001). The first (Zaynoun et al., 1985) was a Lebanese hospital-based study of 262 BCCs (95% from the head and neck), which reported that 93% of BCCs were associated with some degree of solar elastosis. This study also observed that the facial subsites with the greatest proportion of BCCs with moderate/marked solar elastosis were the nose, cheeks and forehead. They also reported that 33% of BCCs had no or at the most, mild solar elastosis, and about half of these BCCs were also from the head and neck. A study of 175 BCCs (58% from the head and neck) diagnosed at assorted primary care and specialist clinics in the northern USA observed only 25% of BCCs to be associated with solar elastosis (Kaur et al., 2006).

**1.4.3.2 Constitutional factors**

**Genetic predisposition**

Several genetic disorders characterised, in part, by the development of multiple BCCs have been described. The study of patients with the autosomal dominant Nevoid Basal Cell Carcinoma syndrome (NBCCS or Gorlin’s syndrome) has shaped the current knowledge about BCC pathogenesis. Typically, NBCCS is distinguished by the childhood onset of multiple BCCs, as well as multisystemic internal tumours, pitting of the palms and soles and dental and brain malformations (Gorlin, 2004). Exposure to
solar UVR likely modifies the risk as 40% of black-skinned NBCCS syndrome patients develop BCC compared to 90% of white-skinned patients (Goldstein et al., 1994). NBCCS patients inherit defective copies of the tumour suppressor patched-1 gene and tumours arise following inactivation of the remaining allele (Wicking and McGlinn, 2001). Similarly, patients with the X-linked dominant Bazex syndrome also develop multiple BCCs among other phenotypic abnormalities including, congenital hypotrichosis and follicular atrophoderma of selected body sites (Bazex et al., 1966). Rombo syndrome, of autosomal dominant inheritance, results in a similar phenotype but BCCs develop later in life (Michaelsson et al., 1981). Xeroderma pigmentosum (XP) is a rare autosomal recessive nucleotide excision repair disorder. Clinically, XP patients’ have extreme photosensitivity to UVR as a result of a defect in any one of the seven genes that regulate excisional repair of UVR-damaged DNA. Skin tumours in XP patients show high levels of ras oncogene activation, Ink4a-Arf and TP53 tumour suppressor gene modifications and aberrations of the sonic hedgehog pathway (Daya-Grosjean and Sarasin, 2005). UV-specific mutations of the smoothened gene are three times higher in XP patients than in those with sporadic BCCs, confirming the high rate of UV-induced mutations in these DNA-repair deficient persons (Couve-Privat et al., 2002). Although mutations in the sonic hedgehog gene are rare in sporadic BCCs, they are found in 15% of BCCs from XP patients (Couve-Privat et al., 2004). The glutathione-S-peroxidase enzyme family is part of the skin’s defence mechanism against UV-induced oxidative stress and polymorphisms in GSTM1, GSTM3, GSTT1 and GSTP1 in particular appear to be associated with increased occurrence of BCC (Lear et al., 1996; Ramachandran et al., 2000).

**Pigmentation phenotype**

Personal physical characteristics can inherently increase a person’s susceptibility to the effects of sun exposure and hence predispose them to BCC. Independent determinants of raised BCC risk include characteristics such as pale complexion, a tendency to sunburn and lack of propensity to tan (see Appendix 3). Two case-control (Gallagher et al., 1995; Walther et al.,
2004) and one cohort study (Green et al., 1996) have found that people with fair skin are at increased risk for BCC compared to those with darker skin. A larger number of independent studies (including one cohort study (van Dam et al., 1999) and seven case-control studies (Kricker et al., 1991; Naldi et al., 2000; Rosso et al., 1996; Rosso et al., 1998; Vlajinac et al., 2000; Walther et al., 2004; Zanetti et al., 2006)) have assessed the predictive value of the skin’s response to sun exposure: people with skin that burns readily but does not tan are consistently reported to be at increased risk for BCC when compared to people with skin that tans readily. With regard to eye and hair colour case-control and cohort studies alike consistently report that people with red hair and often those with blonde hair, or those with blue or green coloured eyes have an increased risk for BCC (see Appendix 3). Just one case-control study failed to find a significant association between hair and eye colour and increased risk for BCC (Gallagher et al., 1995).

*Melanocytic nevi*

Nevi can be defined as pigmented macules or papules of any size and distinguishable from other pigmented lesions on the skin. While it is known that the prevalence of melanocytic nevi is strongly predictive of melanoma occurrence (Chang et al., 2009), the association with BCC is uncertain based on the mixed evidence to date. Two recent Italian case-control studies have reported respectively no association (Zanetti et al., 2006) and a significantly increased risk for BCC on the trunk (Pelucchi et al., 2007), among people with nevi on the upper limbs. A case-control study in Western Australia found that overall risk of BCC rose with increasing nevus counts on the back (Kricker et al., 1991), while the Health Professionals Follow-up Study in the USA showed that nevi on the forearms were modest but significant predictors of risk for BCC (van Dam et al., 1999). Limited prospective data from the Nambour Skin Cancer Study suggested that persons with nevi on the back were at a moderately increased risk of first BCC on the head and neck but not the trunk (Neale et al., 2007).

*Repeated occurrences*
Predictive factors for subsequent BCCs may be important for follow-up regimes but valid prognostic studies are sparse. van Iersel et al. (van Iersel et al., 2005) followed 237 patients and found older age at diagnosis, infiltrative type and BCC with a diameter greater than 1 cm to be risk factors. They found no associations with sex, anatomical site, depth or layer of invasion. These findings are supported by other studies (Ramachandran et al., 2002; Ramachandran et al., 2003). In contrast, a retrospective study of BCC patients found that truncal BCC is associated with significantly more BCCs at this site (Ramachandran et al., 2001). The same group have suggested that different mechanisms determine the development of truncal and nontruncal BCC; they reported that the rate of increase of nontruncal BCCs per year was similar in patients with and without initial truncal lesions (Ramachandran et al., 2001). A study based on Swiss cancer registries indicates that the relative risk of second BCC is greater at younger age, declining with increasing age (Levi et al., 2006). The presentation of multiple BCCs synchronously appears to be a significant predictor of subsequent lesions, and most likely associated with genetic susceptibility (Ramachandran et al., 1999). It is important to note that investigations into factors distinguishing the number of subsequent BCC (single or multiple) are yet to be conducted. To date, however, Marcil and Stern (Marcil and Stern, 2000) have shown that the average proportion of patients developing a subsequent BCC within three years of diagnosis was 44% and that this was strongly associated with the number of previously diagnosed lesions.

### 1.5 Treatment and economic impact

There are a number of treatment modalities available for BCC. The common purpose of each is to remove the tumour whilst maintaining the cosmetic and functional capacity of nearby skin. Surgery is normally the first line of defence. It is performed with either pre-determined margins of normal tissue, by frozen section or the removal of the tumour in layers (Moh’s micrographic surgery). Non-surgical treatments include curettage, cryotherapy,
radiotherapy, phototherapy and topical treatments. The effectiveness of these treatments was addressed in a recent Cochrane review (Bath-Hextall et al., 2007b): surgery and radiotherapy were the most effective treatments for BCC and Moh’s micrographic surgery was the most effective for BCC on facial sub-sites. Cosmetically photodynamic therapy yields better results than surgery or radiotherapy, however, long term follow-up of all photodynamic therapy recipients is needed due to the comparatively high recurrence rate. While cryotherapy is easier to administer it is not as effective as surgery or radiotherapy. The short-term therapeutic efficacy of the topical treatment Imiquimod appears to be effective for superficial BCCs; two ongoing studies will assess the long-term effectiveness of Imiquimod (Gollnick et al., 2005; Quirk et al., 2006).

Skin cancer exerts a considerable national and global disease burden. While BCC accounts for 80% of all skin cancers the associated morbidity and mortality is comparatively minimal, thus its disease burden is what underlies the substantial economic burden of BCC treatment on Western health systems (Joseph et al., 2001). In the United States, some USD 13 billion is spent annually to treat keratinocyte cancers, ranking them among the most costly cancers (Chen et al., 2001). Similarly in England, skin cancers cost GBP 71 million to the National Health Service annually (Morris et al., 2005). In Australia, a recent assessment of treatment for BCC revealed that 22% of patients are referred to a specialist for BCC, while the typical number of doctor visits ranged from 3 to 7, with a range of total cost per patient of AUD $147 to $496, depending on complexity and the need for referral (Streaton et al., 2006). The Australian Federal Government outlays in excess of AUD 180 million per year for BCC treatment alone: in conjunction with squamous cell carcinoma of the skin, these are by far the most expensive cancers treated in Australia (AIHW, 2005). These estimates do not include the health resource consumption associated with benign skin tumours suspected of malignancy or the costs of skin cancer prevention campaigns.
1.6 Comparisons with other skin cancers

Nomenclature

Due to the cellular complexity of the skin, it can give rise to a wide spectrum of epithelial tumours. Based on the causal role of solar ultraviolet radiation, they can be grouped as “sun-induced” and “non-sun-induced” malignancies. The former include basal and squamous cell carcinomas, melanomas, and premalignant lesions such as actinic keratoses and nevi. For many years the term “non-melanoma skin cancer” was used to collectively refer to cutaneous BCC and squamous cell carcinoma (SCC), to reflect their distinction from melanomas. In recent years, however, they have more appropriately been termed “keratinocyte cancers” to reflect their cells of origin.

There is a larger range of non sun-induced tumours yet they are much less frequent. They include adnexal tumours of the four skin appendages, namely the hair follicle, eccrine, apocrine and sebaceous glands; Paget’s disease; Merkel cell carcinoma; and vascular neoplasms (Rigel, 2005). (It has been suggested that Merkel cell carcinoma may be associated with sun exposure (Kampshoff and Cogbill, 2009)). It is not uncommon for these tumours to be misdiagnosed as the more common keratinocyte cancers, however, differentiation is important as they each have different capabilities for local recurrence, invasion and metastasis. These non sun induced skin conditions generally present sporadically, however, familial cases may occur and some individuals may have a genetic predisposition.

1.6.1 Melanoma

Melanoma is the most serious form of skin cancer and Australia has the highest incidence in the world (Parkin and Muir, 1992), especially in Queensland, with an incidence rate of invasive melanomas of 82 per 100 000 persons for males and 55 per 100 000 persons for females (Coory et al., 2006). Although melanoma ranks as the third most common form of skin cancer, behind basal and squamous cell carcinomas, it has a higher mortality
rate because it readily metastasises (Rook, 2004). In recent decades, both incidence and mortality of this highly aggressive cancer have increased (Jemal et al., 2001). Melanomas originate from melanocytes: pigment synthesising cells of neural-crest lineage, which may become malignant as a result of combined genetic, epigenetic and environmental insults. Many factors are known to be independent determinants of melanoma risk, including: physical characteristics such as pale complexion, a tendency to sunburn, lack of propensity to tan and high number of cutaneous naevi (Elwood et al., 1990; Green et al., 1986; Holman et al., 1986). A family or personal history of melanoma, and more commonly, exposure to solar ultraviolet radiation also strongly feature in the development of this cancer. The presence of melanomas on habitually sun-exposed body sites and on skin usually covered by clothing (Elwood and Gallagher, 1983; Green et al., 1993; Whiteman et al., 2007) is explained by the divergent pathway model (Whiteman et al., 2003). This model proposes that for melanomas arising on sun-exposed body sites such as the face and neck, chronic sun exposure drives proliferation of transformed epidermal melanocytes. In contrast, melanomas arising on body sites with unstable melanocyte populations such as the trunk require that exposure to sunlight is early in life and thereafter, host factors drive melanoma development.

### 1.6.2 Squamous cell carcinoma

The second most common skin cancer, squamous cell carcinoma, arises from committed keratinocytes in the epidermal skin layer. They may arise de novo or from actinic keratoses (Frost et al., 2000; Marks et al., 1988). In Australia SCC occurs at a rate of 387 per 100 000 persons and incidence has increased since 1985 when SCC affected an estimated 166 people per 100 000 (Staples et al., 2006). The incidence increases more sharply with age than for BCC (Staples et al., 2006) reflecting the causal role of cumulative sunlight. The phenotypic risk factors for SCC are shared among all three sun-induced skin cancers and they include: fair hair, eye and skin complexion, propensity to burn and inability to tan (English et al., 1998).
Given that some SCCs arise from actinic keratoses, as expected a personal history of these lesions is strongly associated with this skin cancer (English et al., 1998). Actinic keratoses themselves are associated with chronic sun exposure, and their especially strong association with SCC risk is not mirrored to such an extent in either BCC or melanoma. SCC most frequently develops on sun-exposed anatomic sites such as the head and neck and exposed parts of the limbs (Franceschi et al., 1996; Raasch et al., 1998) and there is an inverse relationship between latitude and SCC incidence (Parkin and Muir, 1992; Scotto et al., 1983). A history of sunburns and cutaneous markers of chronic sun exposure (for example, elastosis of skin on the neck) are strong predictors for SCC risk (Green et al., 1996). Other occupational and genetic factors can predispose to SCC.

1.7 Research questions, hypotheses and projected Outcomes

1.7.1 Rationale

As above, the highest reported incidence rates of basal cell carcinoma (BCC) are recorded for Queensland, Australia where 1 to 2 people per 100 are affected annually (Raasch and Buettner, 2002). This skin cancer has a predilection to occur multiply in individuals, either synchronously or over time, and this is observed in populations where BCC incidence is an order of magnitude lower (Bath-Hextall et al., 2007a) (Karagas et al., 1999).

While much is known about the complex constitutional and environmental risk factors for general BCC occurrence (English et al., 1998; Green et al., 1996; Naldi et al., 2000; Zanetti et al., 2006), little is known about their relative importance in multiple BCC occurrences in individuals. Further, there is no agreement on whether there is any relationship between this keratinocyte cancer and the propensity to develop melanocytic naevi, the strongest phenotypic predictor for melanoma (Wachsmuth et al., 2001; Zhu
et al., 1999) (Swerdlow and Green(1987)BJDerm). The association between BCC and its principal environmental risk factor solar UVR ((IARC), 2000) is unclear regarding self-reported recreational UVR and history of high occupational and cumulative UVR exposure (Bastiaens et al., 1998; Gallagher et al., 1995; Green et al., 1996; Marehbian et al., 2007; Zanetti et al., 2006) (English et al., 1998; Kricker et al., 1995). On the other hand, clinical markers of cutaneous sun damage (solar keratoses, telangiectasia and elastosis) are risk factors for general BCC occurrence (Green et al., 1996; Kricker et al., 1991; Marcil and Stern, 2000; Revenga et al., 2004). It has not previously been investigated whether signs of sun damage to the skin are predictors of multiple primary BCCs.

This information arising from and the preceding literature review gives rise to a set of research questions (Table 1) that centre on the epidemiology of BCC. They seek to address these important knowledge gaps within the realm of the Nambour Skin Cancer Study, a longitudinal study of the occurrence and causes of sun-induced skin cancers among a population-based sample of Nambour residents from Queensland, Australia.

<table>
<thead>
<tr>
<th>Research questions and hypotheses</th>
<th>Chapter</th>
<th>Projected outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>2</td>
<td>Up to date report of the overall incidence of BCC and its anatomic distribution among the population of Queensland, Australia. Foundational document for the incidence of people singly and multiply affected by BCC.</td>
</tr>
<tr>
<td>H1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What are the age-standardised incidence rates of primary single and multiple BCCs according to age, sex and anatomic subsite of occurrence during 1997 to 2006?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>That the incidence of single and multiple BCC will increase with advancing age and the male sex. The BCC distribution across anatomic subsites will reflect the associated levels of sun exposure.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R2</td>
<td>What is the association between the propensity for melanocytic nevi on the arms and on the back, and the occurrence of single and multiple BCCs, and their anatomic site of occurrence among people affected more than once?</td>
<td></td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>H2</td>
<td>There is no association between the presence of melanocytic nevi on the arms or back and the occurrence of single or multiple BCCs. Melanocytic nevi on the arms or back will not influence the anatomic site of BCC development.</td>
<td></td>
</tr>
<tr>
<td>R3</td>
<td>Is the association between risk factors for BCC (age, sex, pigmentary traits, sun exposure, sun dose) different among people who are affected by 2-3 or ≥4 BCCs compared to people singly affected?</td>
<td></td>
</tr>
<tr>
<td>H3</td>
<td>People who develop multiple BCCs will have a fairer skin complexion and more evidence of cutaneous sun damage compared to people with a single BCC.</td>
<td></td>
</tr>
<tr>
<td>R4</td>
<td>Are anatomic sites with cutaneous sun damage more likely to develop BCCs than sites without cutaneous sun damage?</td>
<td></td>
</tr>
<tr>
<td>H4</td>
<td>Basal cell carcinomas are more likely to develop on sites with cutaneous sun damage than sites without evidence of cutaneous sun damage.</td>
<td></td>
</tr>
<tr>
<td>R5</td>
<td>What are the common histological growth patterns of basal cell carcinoma in a high risk Australian population?</td>
<td></td>
</tr>
<tr>
<td>H5</td>
<td>The nodular growth pattern will be the most common growth pattern followed by superficial in this series of BCCs.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>A detailed document that describes the association between an individual’s propensity for melanocytic nevi and the acquisition of BCC.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Foundation document that describes the association between putative risk factors (age, sex, pigmentary traits, sun exposure, sun dose) and the acquisition of multiple BCC and the anatomic site of BCC occurrence.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Foundation document detailing the association between BCC risk factors and nodular and superficial BCCs.</td>
<td></td>
</tr>
<tr>
<td>R6</td>
<td>Do nodular and superficial BCCs have the same associations with risk factors (age, sex, pigmentedary traits, sun exposure, sun dose) when compared to people unaffected by BCC?</td>
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</tr>
<tr>
<td>----</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>H6</td>
<td>Nodular and superficial BCCs have similar associations with regard to risk factors when compared to people unaffected by BCC.</td>
<td></td>
</tr>
<tr>
<td>R7</td>
<td>To what extent do BCCs develop on people who have histological evidence of chronic cutaneous sun damage or other clinical signs of actinic skin damage?</td>
<td></td>
</tr>
<tr>
<td>H7</td>
<td>BCCs are associated with a moderate to severe degree of perilesional solar elastosis and persons with these BCCs have some evidence of chronic cutaneous sun damage.</td>
<td></td>
</tr>
</tbody>
</table>

|   | 6 | Foundation document detailing a synthesis of perilesional solar elastosis associated with BCCs and chronic markers of photodamage. |

Table 1: Research questions, their corresponding hypotheses and projected outcomes.
CHAPTER 2

INCIDENCE OF BASAL CELL CARCINOMA

MULTIPLICITY AND DETAILED ANATOMIC DISTRIBUTION: LONGITUDINAL STUDY OF AN AUSTRALIAN POPULATION
2.1 Introduction

The following published manuscript forms the basis of this results chapter. It directly addresses research question R1 (see section 1.7): what are the age-standardised incidence rates of primary single and multiple BCCs according to age, sex and anatomic subsite of occurrence during 1997 to 2006?

2.2 Contribution of the candidate

I conceived and designed the investigation with advice from Prof Adèle Green and Dr Jolieke van der Pols. I developed a set of new variables for the analyses required; they included variables capturing the number of times a person had been affected by BCC during the observation period and person time at risk variables. The remaining variables were available in the existing datasets. I requested pathology reports from the Queensland pathology laboratories for those lesions that did not have data available for the specific anatomic site. I performed most of the data analyses and drafted the manuscript. With input from the other co-authors, I was responsible for all subsequent editing and redrafting and submission of the final manuscript. I prepared the responses to reviewers’ comments with input from Prof Gail Williams, Dr Jolieke van der Pols and Prof Adèle Green.

2.3 Acknowledgement of the contribution of others

All the data included in the following manuscript were collected as part of the Nambour Skin Cancer Study. The Nambour Skin Cancer Study was conceived and designed by the Nambour Skin Cancer Follow-up Study investigators, namely, Prof Adele Green and Prof Gail Williams. Dr Rob Ware calculated the 95% confidence intervals. Nirmala Pandeya and Prof Gail Williams gave advice for the statistical approach using SAS software. Dr Rachel Neale assisted with the editing of the manuscript. Dr Jolieke van der Pols and Prof Adèle Green contributed to the interpretation of the results and assisted with the editing and drafting of the manuscript.
Principal Supervisor Confirmation

The authors listed above have certified that:

1. they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;

2. they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;

3. there are no other authors of the publication according to these criteria;

4. potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit, and

5. they agree to the use of the publication in the student’s thesis and its publication on the Australasian Digital Thesis database consistent with any limitations set by publisher requirements.

I have sighted email correspondence from all Co-authors confirming their certifying authorship.

Adèle C Green

Name       Signature                        Date

2.4 Manuscript: Incidence of Basal Cell Carcinoma

Multiplicity and detailed Anatomic Distribution:

Longitudinal Study of an Australian Population

(Published in Journal of Investigative Dermatology February 2009)
Due to copyright restrictions, this article is not available here. Please consult the hardcopy thesis available from QUT Library or view the published version online at:

http://dx.doi.org/10.1038/jid.2008.234
CHAPTER 3

MELANOCYTIC NEVI AND BASAL CELL CARCINOMA:

IS THERE AN ASSOCIATION?
3.1 Introduction

This results chapter comprises a manuscript that will soon be submitted to an international peer-reviewed journal, and as such is presented here in a general format required for manuscript submission. It directly addresses research question R2 (see section 1.7): what is the association between the propensity for melanocytic nevi on the arms and on the back, and the occurrence of single and multiple BCCs, and their anatomic site of occurrence among people affected more than once?

3.2 Contribution of the candidate

I conceived and designed the investigation with advice from Prof Adèle Green and Dr Jolieke van der Pols. I developed new variables to capture the number of times a person had been affected by BCC during the observation period. The remaining variables were available in the existing datasets. I performed the data analyses and drafted the manuscript. With input from the other co-authors, I was responsible for all subsequent editing and redrafting and submission of the final manuscript. I prepared the responses to reviewers’ comments with input from both co-authors.

3.3 Acknowledgement of the contribution of others

All the data included in the following manuscript were collected as part of the Nambour Skin Cancer Study. The Nambour Skin Cancer Study was originally conceived and designed by the Nambour Skin Cancer Study principal investigator, Prof Adèle Green. Dr Jolieke van der Pols and Prof Adèle Green contributed to the interpretation of the results and assisted with the editing and drafting of the manuscript.

Principal Supervisor Confirmation

The authors listed above have certified that:
1. they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
2. they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
3. there are no other authors of the publication according to these criteria;
4. potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit, and
5. they agree to the use of the publication in the student’s thesis and its publication on the Australasian Digital Thesis database consistent with any limitations set by publisher requirements.

I have sighted email correspondence from all Co-authors confirming their certifying authorship.

Adèle C Green

Name       Signature                        Date

3.4 Manuscript: Melanocytic nevi and basal cell carcinoma: is there an association?
Title
Melanocytic nevi and basal cell carcinoma: is there an association?

Authors
Naomi M Richmond-Sinclair ¹, ²
Jolieke C van der Pols ¹
Adèle C Green ¹

1. Cancer and Population Studies Unit, The Queensland Institute of Medical Research, Brisbane, Queensland, Australia;
2. School of Life Sciences and Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Queensland, Australia;

Where the work was done
The work was done in Brisbane City in the state of Queensland in Australia

Short title
Melanocytic nevi and basal cell carcinoma

Abbreviations
BCC, basal cell carcinoma
OR, odds ratio
CI, confidence interval
Financial support: This project was supported by a grant from the National Health and Medical Research Council (grant number 442976). Naomi Richmond-Sinclair was supported by a Smart State PhD Scholarship, an ANZ Trustees Medical Research in Queensland PhD Scholarship and Queensland Institute of Medical Research PhD Top-Up Scholarship.

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Abstract

It is important to establish the existence and magnitude of the association between melanocytic nevi and basal cell carcinoma (BCC) to give possible insights into shared pathways of solar ultraviolet tumorigenesis. We investigated this in a community-based Australian study with 21 years of follow-up. Dermatologists counted nevi on the forearms (1986) and back (1992), and BCC frequency and sites were prospectively monitored to 2007.

Of 1621 study participants at baseline (1992), 1339 (mean age 49-years; 56% women) had complete follow-up. Of those followed up, 401 (30%) had a total of 1202 histologically-confirmed BCCs. After adjustment for age, sex, skin color, nevi on the back, and sun exposure, BCC risk increased significantly in those with forearm nevi (odds ratio (OR), 1.5; 95% confidence intervals (CI), 1.1-1.9). For BCC on the back, risk was doubled in those with many (11 or more) forearm nevi compared with no forearm nevi (OR=2.4; 95%CI 1.1-4.8). Nevi on the back were not associated with subsequent BCC. This suggests that high site-specific nevus prevalence, reflecting both a nevus propensity and high sun exposure early in life, influences future BCC development.
Introduction

Although both basal cell carcinoma (BCC) and cutaneous melanoma are caused by exposure to solar ultraviolet radiation (International Agency for Research on Cancer, 1992), they are considered unusual because in general their relationship with sun exposure is not dose-dependent (Rosso et al., 1998). They have broadly similar body site distributions with a substantial proportion of both tumors occurring on the back as well as the face (Neale et al., 2005), and both have relatively young ages of onset (Richmond-Sinclair et al., 2009; Siskind et al., 2005). Skin pigmentary factors indicating sun-sensitivity determine risks of both BCC and melanoma (English et al., 1998; Green et al., 1996; Naldi et al., 2000; Siskind et al., 2005) and some molecular profiles are common to both (Greinert, 2009). While it is known that the prevalence of melanocytic nevi is strongly predictive of melanoma occurrence (Chang et al., 2009), the association with BCC is uncertain based on the mixed evidence to date. Two recent Italian case-control studies have reported respectively no association (Zanetti et al., 2006) and a significantly increased risk for BCC on the trunk (Pelucchi et al., 2007), among people with nevi on the upper limbs. A case-control study in Western Australia found that overall risk of BCC rose with increasing nevus counts on the back (Kricker et al., 1991), while the Health Professionals Follow-up Study in the USA showed that nevi on the forearms were modest but significant predictors of risk for BCC (van Dam et al., 1999). We ourselves have previously reported some limited prospective data from the Nambour Skin Cancer Study suggesting that persons with nevi on the back were at a moderately increased risk of first BCC on the head and neck but not the trunk (Neale et
al., 2007). In this report we have substantially lengthened the period of follow-up of the Nambour Study cohort to two decades and have now investigated the association between prevalence of melanocytic nevi on the forearms as well as nevi on the back and the occurrence of histologically confirmed BCC.
Results

There were 1339 participants who had complete follow-up until either death (102, 8%) or end of observation on 31 December 2007 (1237, 92%). At baseline in 1992 their mean age was 49 years, 56% were women and 18% had a past history of BCC. During the 16-year observation period 401 individuals (207 women, 194 men), had a total of 1202 primary histologically-confirmed BCCs. Of these, 169 (100 women, 69 men) developed a single primary BCC while the remaining 232 (58%) (107 women, 125 men) developed multiple primary BCCs. Average age at diagnosis of a first BCC in the study period was 61 years (60 for women, 61 for men).

Among all participants, 1162 people (87%) had nevi either on the forearms in 1986 or the back in 1992. Nevi on the forearms were present in 530 participants of whom 56 (11%) had no nevi on the back (14 people did not have data available for nevi on the forearms). Nevi on the back were present in 1092 participants of whom 618 (57%) had no nevi on the forearms. 25 people had 11 or more nevi on the arm as well as the back. Among those with any nevi on the forearms slightly more were female (358, 68%) compared to the proportion of females among those with nevi on the back (608,56%; (p=<0.001), but age distributions were similar (Table 1). Regardless of whether people had nevi on one or both sites, the proportion of people affected by BCC (including multiple BCCs) was the same for each group (Table 2).
People with nevi present on the forearms in 1986 were more likely to be affected by BCC during the follow-up study period 1992-2007 compared to those without nevi on the forearms (OR=1.5, 95%CI 1.1-1.9), and the same was found for each nevus-count category (Table 2). We separately analysed people with a single BCC and those with multiple BCCs and found that presence of forearm nevi was more strongly associated with multiplicity of BCC (OR=1.6, 95%CI 1.2-2.2) than with occurrence of a single BCC (OR=1.4, 95%CI 0.94-2.0) in the follow-up period (Table 2). There was no consistent association between numbers of nevi on the back in 1992 and subsequent occurrence of BCC (Table 2). There was no association between BCC and the presence of any nevi on back or forearms versus no nevi (OR=1.1, 95%CI 0.80-1.6).

We further assessed whether there was an association between the anatomic site of BCC and number of nevi on the forearms or on the back. The presence of nevi on the forearms was associated with BCC on the head and neck (OR=1.5, 95%CI 1.1-2.1) and BCC on the trunk (OR=1.7, 95%CI 1.2-2.5), but not with BCC on the limbs (Table 3). Neither combined-sites nevus counts (data not shown) nor nevi on the back were associated with BCC at any specific anatomic site (Table 3).
Discussion

In this prospective study with 21 years of follow-up, we have shown that the presence of nevi on the forearms is associated with an increased occurrence of BCC overall and also with multiple occurrences of primary BCC over time. With regard to sites of occurrence of BCC, people with many forearm nevi had a modestly raised risk of BCC on the typically sun-exposed head and neck and had an even higher (doubling) of risk for BCC on the trunk, compared with people who had no nevi on the forearms. BCC on the limbs was not related to nevi on the forearms however. In contrast to the observations for nevi on the arm, nevi on the back in general showed no association with BCC occurrence.

The findings of this study are consistent with those of another prospective study that has investigated the association between nevi and BCC occurrence in the USA (van Dam et al., 1999). That study reported a modestly raised risk of BCC in male health professionals who had any nevi on their forearms, with no effect of number of nevi. Our results are also similar to those of a hospital-based case-control study of a Southern European population where people affected with BCC had an increased number of nevi on the forearms overall, again with no increased risk with increasing numbers of nevi (Naldi et al., 2000). On the other hand, a Western Australian case-control study showed a non-significant increase in odds ratios for BCC overall with increasing counts of nevi on the back.
(Kricker et al., 1991), and yet other case-control studies have found no association (Vlajinac et al., 2000; Zanetti et al., 2006).

Nevi mostly develop during childhood and adolescence (Crane et al., 2009). They are influenced by habitual childhood (Green et al., 1988b) and adolescent sun exposure (Darlington et al., 2002). Twin studies in restricted geographic locations reinforce the importance of genetic and environmental factors (Wachsmuth et al., 2001; Zhu et al., 1999). Although the etiology of melanocytic nevi is incompletely understood we have previously suggested that there is site-dependent susceptibility to melanocytic changes: that melanocytes on the trunk require less cumulative sun exposure than melanocytes of the head and neck or the arms to undergo change (Green, 1992). The fact that nevi on the forearms but not nevi on the back predict the multiple occurrence of BCC over time leads us to speculate that there is more than simple nevus propensity playing a role, and that it is the amount of sun exposure early in life (Green et al., 1988b; MacLennan et al., 2003), namely the first two decades, that is influencing BCC risk. Whilst nevi on the forearms appear to reflect high childhood sun exposure (Darlington et al., 2002) clearly it is not sufficient for BCC development later in life. This study did not investigate the association between solar lentigines, another type of benign pigmented lesion that occurs on sun-exposed areas of the skin and are associated with ageing (Chen et al., 2010; Yaar and Gilchrest, 2007). Unlike nevi, one would expect a priori a positive association between solar lentigines, as indicators of cumulative sun exposure with age, and BCC, and indeed this is what we have previously observed in this population (Neale et
We conclude the combined effects of ultraviolet radiation received early in life and during adult life lead to BCC pathogenesis.

The present findings and other longitudinal data may point to an intriguing commonality of genetic risk factors between nevi and BCC (e.g. frequency of UVB-induced genetic lesions (Wang et al., 2005) since it is highly unlikely that forearm nevi per se could directly influence BCC occurrence given the difference in target cell type and the lack of association of BCC with nevi on the trunk.

A limitation to be considered in the interpretation of the comparisons between the associations of BCC with forearm nevi on one hand and back nevi on the other, is that the counts of nevi on forearms and on the back were made some 5 years apart (end of 1986 and start of 1992 respectively). Because it is believed that nevi involute as adults grow older (Bataille et al., 2007; Green and Swerdlow, 1989), it is likely that the absolute nevus counts on the back would have been higher had they been recorded in 1986. Indeed a small proportion of people with nevi present on the back in 1986 may have been classified as having no nevi on the back in 1992 due to the natural history of nevi. While it seems unlikely that this bias could wholly explain the qualitatively different associations of forearm versus back nevi with BCC, it is possible that it influenced the relative magnitude of the associations reported here. We also considered the possibility that there may be a differential biopsy rate of limb BCCs among individuals who had nevi on the forearms compared to those who did not. The lack of association between nevi on the
forearms and BCC on the limbs (predominantly the arms) in our data does not support this. Nor did we find that nevi on the back were associated with BCC on the back.

In summary our results indicate that people with nevi on the forearms were significantly more likely to be affected by BCCs during the two decades of follow-up than people without nevi on the forearms. People with nevi on the back were not at increased risk of subsequent BCC however. This increase in risk of BCC was particularly strong for multiple primary BCCs over the two decades of follow-up, and was specific for BCCs on the head and especially the trunk.
Materials and methods

At baseline in 1986, 2095 residents of the subtropical Queensland township of Nambour (latitude 26°S) were randomly selected from the electoral register of all adults in the township (Green et al., 1988a). Between 1992 and 1996, 1621 of these adults (77%) participated in a field trial to assess daily sunscreen application and beta-carotene supplementation in the prevention of skin cancer (Green et al., 1999). After the trial, follow-up of skin cancer continued (van der Pols et al., 2006) till 2007. Ethical approval was obtained from the ethics committee of the Queensland Institute of Medical Research.

In 1986 dermatologists recorded the number of melanocytic nevi greater than 2mm in diameter, raised or flat, on participants’ forearms and hands (hereafter referred to simply as forearms). Nevi on participants’ backs were similarly recorded in 1992, and all participants completed a baseline standard questionnaire about pigmentary traits and sun exposure history. Regarding the latter, participants reported both their occupational and recreational sun exposure as mainly outdoors/mainly indoors/ or mixed indoors, outdoors. Detailed information about all skin cancers that occurred from 1992 to 1996 was collected during 3 separate full-body skin examinations conducted by dermatologists (Green et al., 1996; Green et al., 1999). Following the trial, participants consented to have pathology records of all further skin cancers made available to the investigators allowing virtually complete ascertainment of histologically-confirmed BCCs through regional pathology laboratories.
Because the same BCC may be histologically confirmed twice, at initial biopsy/excision and again if re-excised, all records of apparently multiple BCCs verified within a 6-month period in the same person on the same anatomical site were cross-checked to identify duplicate reports. Recurrent BCCs diagnosed at the sites of earlier primary lesions were excluded.

**Data analysis**

Only people who experienced a new histologically-diagnosed BCC during the study period, 1992 to 2007, were considered cases. We did not exclude those people who had a BCC prior to the observation period because the BCC records for that time were incomplete for some participants. We can therefore only be certain about the BCC status of all participants for the 16-year observation period. For investigation of the number of BCCs that participants developed, analyses were person-based and affected participants were classified according to the number of BCCs they developed in the 16-year study period: none, one, or multiple primary BCCs (synchronously or over time). Anatomic site analyses were lesion-based such that for analyses of associations with BCCs occurring on the head and neck, all people without a BCC constituted the reference group. Thus while the sites of occurrence of individual BCCs were mutually exclusive, the sites of BCC occurrence within multiply-affected individuals were not, in the sense that they could contribute BCCs to several sites.
Nevus counts were recorded as categorical variables and used to estimate odds ratios (OR) with 95% confidence intervals (CI). Multivariate logistic regression was used to assess the association of nevi on the forearms or on the back with the development of BCC. Analyses of associations with nevi on the forearm (or back) were adjusted for age, sex, skin color as evaluated by a dermatologist, self-reported skin response to acute sun exposure, occupational sun exposure and recreational sun exposure (categorised as above), randomised sunscreen treatment group during the field trial, and presence of nevi on the back (or forearm). Occupational and recreational sun exposure, the predominant determinants of the scale of adult sun exposure, were accounted for in all analyses relating to BCC development. Statistical analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina) and SUDAAN 10 (RTI Institute, Research Triangle Park, North Carolina).
Conflict of Interest

The authors state no conflict of interest

Acknowledgements

We thank the Nambour Skin Cancer Study participants themselves and their doctors who assisted in long-term monitoring of skin cancer. Many volunteer helpers from the Nambour community have given their invaluable support to these studies. We are grateful to Dr N. Pandey for expert statistical assistance with data analysis.
References


Table 1: Distribution of age and sex of participant according to melanocytic nevi on the back and forearms

<table>
<thead>
<tr>
<th>Participant characteristics</th>
<th>Nevi on the forearms in 1986</th>
<th>Nevi on the back in 1992</th>
<th>Single BCC</th>
<th>Multiple BCC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 40 years</td>
<td>166 (21%)</td>
<td>185 (35%)</td>
<td>41 (19%)</td>
<td>313 (29%)</td>
</tr>
<tr>
<td>40 to 59 years</td>
<td>374 (47%)</td>
<td>273 (51%)</td>
<td>94 (44%)</td>
<td>539 (49%)</td>
</tr>
<tr>
<td>60 years or older</td>
<td>253 (32%)</td>
<td>72 (14%)</td>
<td>79 (37%)</td>
<td>240 (22%)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>382 (52%)</td>
<td>358 (68%)</td>
<td>129 (60%)</td>
<td>608 (56%)</td>
</tr>
<tr>
<td>Male</td>
<td>411 (48%)</td>
<td>172 (32%)</td>
<td>85 (40%)</td>
<td>484 (44%)</td>
</tr>
</tbody>
</table>
Table 2: Odds ratios* for BCC 1992 to 2007 according to melanocytic nevi on the back and forearms in 1992

<table>
<thead>
<tr>
<th>Participant characteristics</th>
<th>No BCC (n=928)</th>
<th>Single BCC (n=169)</th>
<th>Multiple BCCs (n=232)</th>
<th>At least one BCC</th>
<th>Single BCC</th>
<th>Multiple BCCs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nevi on the forearms in 1986</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>555 (60%)</td>
<td>98 (59%)</td>
<td>140 (61%)</td>
<td>1.0 Ref</td>
<td>1.0 Ref</td>
<td>1.0 Ref</td>
</tr>
<tr>
<td>1-10</td>
<td>318 (34%)</td>
<td>54 (32%)</td>
<td>74 (32%)</td>
<td>1.4 (1.1, 1.9)</td>
<td>1.2 (0.83, 1.8)</td>
<td>1.6 (1.1, 2.3)</td>
</tr>
<tr>
<td>11 or more</td>
<td>55 (6%)</td>
<td>14 (8%)</td>
<td>15 (7%)</td>
<td>1.8 (1.0, 3.0)</td>
<td>1.8 (0.93, 3.6)</td>
<td>1.7 (0.86, 3.3)</td>
</tr>
<tr>
<td><strong>Nevi on the back in 1992</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>148 (16%)</td>
<td>18 (11%)</td>
<td>48 (21%)</td>
<td>1.0 Ref</td>
<td>1.0 Ref</td>
<td>1.0 Ref</td>
</tr>
<tr>
<td>1-10</td>
<td>592 (64%)</td>
<td>129 (79%)</td>
<td>149 (66%)</td>
<td>1.2 (0.83, 1.7)</td>
<td>1.9 (1.1, 3.3)</td>
<td>0.87 (0.59, 1.3)</td>
</tr>
<tr>
<td>11 or more</td>
<td>178 (19%)</td>
<td>17 (10%)</td>
<td>27 (12%)</td>
<td>0.76 (0.47, 1.2)</td>
<td>1.0 (0.5, 2.1)</td>
<td>0.67 (0.38, 1.2)</td>
</tr>
<tr>
<td><strong>Nevi on the forearms or back</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>117 (13%)</td>
<td>15 (9%)</td>
<td>44 (19%)</td>
<td>1.0 Ref</td>
<td>1.0 Ref</td>
<td>1.0 Ref</td>
</tr>
<tr>
<td>1-10</td>
<td>697 (74%)</td>
<td>132 (79%)</td>
<td>163 (70%)</td>
<td>1.2 (0.82, 1.7)</td>
<td>1.9 (1.1, 3.4)</td>
<td>0.91 (0.60, 1.4)</td>
</tr>
<tr>
<td>11 or more</td>
<td>124 (13%)</td>
<td>21 (12%)</td>
<td>25 (11%)</td>
<td>1.0 (0.64, 1.6)</td>
<td>1.5 (0.74, 2.9)</td>
<td>0.84 (0.50, 1.4)</td>
</tr>
</tbody>
</table>

* Adjusted for age as a continuous variable, sex, randomised sunscreen treatment (daily sunscreen application or discretionary use during field trial), skin response to acute sun exposure (tan, burn then tan, burn) and occupational type and recreation type (both
variables are categorised as mainly indoors, indoors and outdoors, mainly outdoors) and naevi on the back or forearms as appropriate (no, 1-10, 11 or more); ‡ CI, confidence interval.

Table 3: Odds ratios* for site-specific‡ BCC 1992 to 2007 according to melanocytic naevi on the back and forearms in 1992

<table>
<thead>
<tr>
<th>Participant characteristics</th>
<th>Distribution of cases (count (%))†</th>
<th>Head and neck</th>
<th>Trunk</th>
<th>Limbs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No BCC (n=928)</td>
<td>Head and neck (n=271)</td>
<td>Trunk (n=173)</td>
<td>Limbs (n=135)</td>
</tr>
<tr>
<td>Nevii on the forearms in 1886</td>
<td>No</td>
<td>555 (60%)</td>
<td>389 (64%)</td>
<td>204 (62%)</td>
</tr>
<tr>
<td></td>
<td>1-10</td>
<td>318 (34%)</td>
<td>182 (30%)</td>
<td>100 (31%)</td>
</tr>
<tr>
<td></td>
<td>11 or more</td>
<td>55 (6%)</td>
<td>42 (7%)</td>
<td>24 (7%)</td>
</tr>
<tr>
<td>Nevii on the back in 1992</td>
<td>No</td>
<td>148 (16%)</td>
<td>103 (17%)</td>
<td>75 (23%)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>770 (84%)</td>
<td>502 (83%)</td>
<td>248 (77%)</td>
</tr>
</tbody>
</table>

* Adjusted for age as a continuous variable, sex, randomised sunscreen treatment (daily sunscreen application or discretionary use during field trial), skin response to acute sun exposure (tan, burn then tan, burn) and occupational type and recreation type (both variables are categorised as mainly indoors, both indoors and outdoors, mainly outdoors) and naevi on the back or forearms as appropriate (no, 1-10, 11 or more); ‡ The site-based sub-groups are not mutually exclusive; persons with BCC on the head and neck and trunk and limbs were analysed as ‘affected persons’ for each anatomic region; * CI, confidence interval.
CHAPTER 4

CLINICAL SIGNS OF PHOTODAMAGE ARE ASSOCIATED WITH BASAL CELL CARCINOMA
MULTIPLICITY AND SITE: A 16-YEAR LONGITUDINAL STUDY
4.1 Introduction

This results chapter comprises a manuscript that has been accepted for publication by the International Journal of Cancer and as such is presented here in the accepted preprint format. It directly addresses research questions R3 and R4 (see section 1.7): is the association between risk factors for BCC (age, sex, pigmentary traits, sun-exposure, sun dose) different among people who are affected by 2-3 or ≥ 4 BCCs compared to people singly affected? And are anatomic sites with cutaneous sun damage more likely to develop BCCs than sites without cutaneous sun damage?

4.2 Contribution of candidate

I conceived and designed the investigation with advice from Prof Adèle Green. I performed the data analyses and drafted the manuscript. I constructed a set of new variables for the analyses; they included variables capturing the number of times a person had been affected by BCC during the observation period and time-dependent variables for sun exposure and sun damage that related to the persons and the lesion. The remaining variables were available in the existing datasets. I requested pathology reports from the Queensland pathology laboratories for those lesions that did not have data available for the specific anatomic site and assisted with the data entry for this information.

4.3 Acknowledgement of the contribution of others

All the data included in the following manuscript were collected as part of the Nambour Skin Cancer Study. The Nambour Skin Cancer Study was conceived and designed by the Nambour Skin Cancer Follow-up Study investigators, namely, Prof Adèle Green and Prof Gail Williams. Nirmala Pandeya and Prof Gail Williams gave advice for the statistical approach using SAS and SUDAAN software. Dr Rachel Neale assisted with the editing of the manuscript. Dr Jolieke van der Pols and Prof Adèle Green contributed
to the interpretation of the results and assisted with the editing and drafting of the manuscript.

Principal Supervisor Confirmation

The authors listed above have certified that:

1. they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
2. they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
3. there are no other authors of the publication according to these criteria;
4. potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit, and
5. they agree to the use of the publication in the student’s thesis and its publication on the Australasian Digital Thesis database consistent with any limitations set by publisher requirements.

I have sighted email correspondence from all Co-authors confirming their certifying authorship.

Adèle C Green

Name       Signature                        Date

4.4 Manuscript: Clinical signs of photodamage are associated with basal cell carcinoma multiplicity and site: a 16-year longitudinal study

(Accepted for publication in International Journal of Cancer 2009)
Title: Clinical signs of photodamage are associated with basal cell carcinoma multiplicity and site: a 16-year longitudinal study

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         Gail M Williams 3
         Rachel Neale 1
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Keywords (MeSH terms): basal cell carcinoma, Australia, prospective studies

Abbreviations: BCC, basal cell carcinoma OR, odds ratio
CI, confidence interval SK, solar keratosis

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Conflict of interest: The authors state no conflict of interest.

Journal category: Epidemiology

Short title: Photodamage associated with multiple basal cell carcinomas
Statement about novelty:

Using evidence from a 20 year prospective Australian study we demonstrate that among those newly affected by BCC, chronic cutaneous sun damage predicts those who will be affected by more than one BCC, while chronic sun damage on the head and neck, trunk and limbs predicts BCC occurrence at each site respectively.

Statement about novelty:

These findings suggest that control of BCC multiplicity in the population at large is feasible through decreasing cumulative sun exposure, thereby helping to curb the substantial encumbrance that BCC places on health systems serving white populations. Follow-up of BCC patients requires thorough whole body skin examinations, rather than being limited to typically sun-exposed sites or to sites previously affected by BCCs.
Abstract

Although sun exposure is known to be associated with basal cell carcinoma (BCC), it is not known what determines multiple occurrences of BCCs among sporadically affected individuals or why BCCs develop on uncommonly sun-exposed body sites like the trunk. In a prospective community-based skin cancer study in Queensland, Australia, we studied all participants who experienced a histologically-confirmed BCC from 1992 to 2007. Sun exposure history was monitored and dermatologists documented phenotype at baseline and signs of photodamage over the study period. Anatomic sites of all incident BCCs were recorded. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using logistic regression. Of 401 participants who developed a new BCC during the 16-years of follow-up, 232 (58%) developed more than one. Male sex (OR=2.5, 95%CI 1.5-5.3) and age 60 or over (OR=4.2, 95%CI 1.5-11.8) but not skin type were associated with highest BCC counts among those affected. Participants with high numbers of solar keratoses were most likely to experience the highest BCC counts overall (OR=4.3, 95%CI 1.4-13.5). Moreover occurrences of BCC on the trunk (OR=3.3, 95%CI 1.4-7.6) and on the limbs (OR=3.7, 95%CI, 95%CI 2.0-7.0) were strongly associated with high numbers of solar keratoses on these sites respectively. Among those newly affected by BCC, chronic cutaneous sun damage predicts those who will be affected by more than one BCC, while chronic sun damage on the trunk and limbs predicts BCC occurrence on the trunk and limbs respectively.
Introduction

The commonest cancer, basal cell carcinoma (BCC), occurs more than once, in a high proportion of individuals sporadically affected. In North American study populations with relatively low incidence of BCC, two prospective cohort studies reported that around 34% of affected people developed multiple BCCs within 5-years of follow-up. In a high incidence Australian population, nearly 50% of affected people developed multiple BCCs over 10-years. Hence it is not only the number of people affected but also the multiple tumors they develop that underlies the substantial health expenditure attributed to BCC treatment in North America, Europe, and Australia.

A limited number of previous studies in selected clinical populations have suggested that multiple BCC occurrence is associated with increasing age, male sex and fair skin, but little is known about the importance of other pigmentary and environmental factors including sun exposure history and photodamage.

Another unanswered question about BCC is why a sizable proportion occur on sites that are often sun-protected like the trunk and limbs, given BCC’s strong association with sun exposure. Some have suggested different mechanisms of BCC pathogenesis on different sites because head/neck BCCs appeared more strongly associated with a sun-sensitive phenotype than trunk BCCs. Also people initially affected by trunk BCC were reported to be affected more often subsequently on the trunk than people with an initial head/neck BCC. Overall, however, there is limited evidence about where on the body successive BCCs arise.
among people affected more than once \(^9,^{16,17}\) and factors underlying BCC's site
distribution in general remain uncertain.

In order to answer these questions we monitored the occurrence of all BCCs
in a subtropical Australian community from 1992 to 2007. We examined the
anatomic sites of BCC occurrence and assessed in detail the associations between
pigmentary traits and various measures of sun exposure with BCC multiplicity. We
hypothesised that people who develop multiple BCCs would have a more sun-
sensitive phenotype than people with a single BCC during the same period.
Material and methods

The Nambour Skin Cancer Study

Study participants were originally randomly selected in 1986 from the electoral register of all adult residents of the subtropical township of Nambour in Queensland, Australia (latitude 26°S) for a baseline study of skin cancer. 2095 people (70%) took part and were shown to be a representative sample of the community with regard to risk factors for skin cancer. Of these, 1621 (77%) participated in a field trial between 1992 and 1996 to assess sunscreen application and betacarotene supplementation in the prevention of skin cancer. Detailed descriptions of the community sample, field trial and its long-term outcomes have been published previously. On conclusion of the trial in 1996, participants were invited to take part in a further follow-up study of skin cancer. Continuing participants consented to have subsequently diagnosed skin cancers notified to the investigators by regional pathology laboratories in Queensland, allowing 100% ascertainment of all histologically confirmed BCCs. No participants were immuno-compromised, and none had nevoid basal cell carcinoma syndrome. Follow-up of skin cancers continued to the end of 2007. Ethical approval was obtained from the ethics committee of the Queensland Institute of Medical Research.

Data collection

Pigmentary traits, sun exposure and photodamage
Participants’ head, neck, arms and hands were examined at baseline in 1986 by dermatologists who documented standard signs of cumulative photodamage (telangiectasia of the face, elastosis of the neck, solar lentigines and solar keratoses) and number of melanocytic nevi on arms. All participants completed a baseline standard questionnaire about pigmented traits (hair and eye color) and sun-exposure habits (occupational and recreational, and sunscreen use when in the sun). At the start of the trial in 1992 participants again completed a standard questionnaire including their skin response to acute sun exposure. In 1992, 1994 and 1996 information about sun exposure was updated by questionnaire and dermatologists carried out full skin examinations. From 1997 to 2007, participants reported their sunscreen use each year and based on their responses were classified as regular or irregular sunscreen users\textsuperscript{21}.

**Basal cell carcinomas**

All BCCs were verified histologically. Because the same BCC may be histologically confirmed twice, at initial biopsy/excision and again if re-excised, all records of apparently multiple BCCs verified within a 6-month period in the same person and on the same anatomic site were cross-checked to identify duplicate reports. Recurrent BCCs diagnosed at the sites of earlier primary lesions were excluded.

**Data management**

**Cases and tumors**
Only people who experienced a new histologically-diagnosed BCC during the study period, 1992 to 2007, were included in the analyses. For investigation of the number of BCCs that participants developed, analyses were person-based and affected participants were classified according to the number of BCCs they developed in the 16-year study period: one; 2-3; 4 or more (synchronously and/or over time). Anatomic site analyses were lesion-based such that for analyses of associations with BCCs occurring on the head/neck, all BCCs that occurred on the trunk or limbs constituted the reference group. Thus while the sites of occurrence of individual BCCs were mutually exclusive, the sites of BCC occurrence within multiply-affected individuals were not, in the sense that they could contribute BCCs to several sites.

**Time-dependent exposures**

For person-based analyses, only sun exposure and photodamage data prior to the date of diagnosis of an individual’s first BCC were used; for tumor-based analyses, all exposures predated diagnosis of each BCC when more than one BCC occurred. For example, for a BCC diagnosed in 1995 the extent of photodamage was taken as the greatest recorded in either 1986, 1992 or 1994 (but not 1996). The responses used for recreational and occupational sun exposure analyses always reflected the level of these exposures reported for the majority of time prior to BCC diagnosis.

**Statistical analysis**
Multivariate polytomous and repeated-measures binomial logistic regression were used to assess the associations between factors of interest and BCC multiplicity and site of occurrence among those affected, respectively. The repeated-measures analyses accounted for the intra-person correlation of BCCs on different sites from the same person. Each exposure variable was treated categorically to estimate the odds ratio (OR) with 95% confidence intervals. All analyses were adjusted for age, sex and randomised sunscreen treatment during the trial. Models also included pigmentary traits and sun exposure variables where appropriate. Statistical analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina) and SUDAAN 10 (RTI Institute, Research Triangle Park, North Carolina).
Results

Study population

During the 16-year observation period 401 participants (30%) of the overall Nambour study cohort, had at least one surgically-excised, histologically-confirmed BCC. Of these 401, 66 had a history of BCC prior to 1992. During the study period approximately equal proportions of women (207; 52%) and men (194; 48%) were diagnosed with an incident BCC, with an average age at diagnosis of the first BCC in the study period of 60-years for women and 61-years for men. The average age at diagnosis of a first BCC was the same for those who developed one or more than one BCC (mean age 60-years). As anticipated, a high proportion of cases had a sun-sensitive phenotype: 62% had fair skin color, 49% had blue/grey eyes and 60% had a light hair color (Table 1).

Among those with a new BCC in the 16-year period, 169 people developed one BCC only (42%; 100 women and 69 men) and 232 people developed more than one BCC (107 women and 125 men), representing a cumulative incidence of multiple BCC of 58%. Among those people who experienced more than one BCC, 61 (26%) had 3 BCC tumors, 31 (13%) had 4 BCC tumors and 13 (6%) had 5 or more (up to 37) BCC tumors. A total of 1202 new BCCs were excised from the 401 affected individuals between 1992 and 2007.

Associations with BCC multiplicity among those affected by BCC
People with multiple BCCs in the study period, synchronously and/or over time, were more likely to be older and male than those with a single BCC. Specifically, those aged 60-years or older at the start of observation were more likely to develop ≥4 BCCs (OR 4.2, 95% CI 1.5-11.8) compared to people younger than 40-years. Males were more likely than females to be affected by 2-3 BCCs (OR 1.8, 95%CI 1.1-3.2) and ≥4 BCCs (OR 2.8, 95%CI 1.5-5.3) among all affected by BCC in the study period (Table 1).

Compared with cases who tanned, cases who had skin that always burnt upon exposure to the summer sun were not more likely to develop multiple BCCs (Table 1). Cases with light eye color were more likely to develop multiple BCCs compared to cases with dark eyes, though this was significant only for people with hazel/green eyes who developed 2-3 BCCs (OR 2.5, 95%CI 1.0-6.5). Whilst presence of melanocytic nevi on the arms was not associated with multiple BCCs, cases with nevi on the back were significantly less likely to develop multiple BCCs (2-3 BCCs: OR 0.39, 95%CI 0.18-0.84, ≥4 BCCs OR 0.29, 95%CI 0.12-0.67, Table 1). No association was found between recreational or occupational sun exposure and BCC multiplicity (Table 1).

Regarding measures of acute photodamage, number of lifetime sunburns reported prior to BCC diagnosis was not associated with multiplicity of BCC among cases (Table 1) and nor were facial telangiectasia and solar elastosis of the neck, as measures of chronic photodamage (Table 1). Among all those affected by BCC, strong associations with increasing BCC multiplicity were evident for increasing total body SK counts such that for those with 5 or more SKs the odds for developing ≥4
BCCs over the observation period were 4 times greater (OR 4.3, 95%CI 1.4-13.5) compared to those with no SKs (Table 1).

**Pattern of anatomic sites affected by BCC**

Among the 169 study participants affected only once by BCC in the study period, nearly half were affected on the head/neck (47%) followed by the trunk or limbs (29% and 24% respectively; Figure 1). Among the 232 participants with more than one BCC, 140 people (60%) were affected on more than one anatomic site. Of the 139 who developed 2-3 BCCs, the most common site combination within an individual was both the head/neck and trunk affected. However, among the 93 who developed ≥4 BCCs, the tumors usually occurred across all the three anatomic sites specified (Figure 1). Among cases multiply affected, 192 (83%) people experienced at least one BCC on the head/neck region, 126 (54%) at least one BCC on the trunk and 75 (32%) at least one BCC on the limbs. Overall the pattern of tumor occurrence across anatomic sites was similar, whether cases had a single BCC or multiple BCCs, with the head/neck by far the most commonly affected site (Figure 1).

**Associations with anatomic site of BCC**

Among all newly affected by BCC in the period, neither age nor sex was significantly associated with the anatomic site of BCC development (Supplementary Table 1).
Cases with facial telangiectasia were more likely to develop BCCs on the head/neck (OR 2.1, 95%CI 1.0-4.1) compared to cases with no facial telangiectasia (Table 2). The presence of many solar lentigines on the face was also associated with BCC on the head/neck (OR 1.8, 95%CI 1.0-3.2) but solar elastosis of the neck was not (Table 2). Cases with 5 or more SKs on the face were more likely to have BCC on the head/neck (OR 2.0, 95%CI 1.1-3.7) compared to cases without SKs on the face. Similarly, cases with increasing numbers of SKs on the trunk were increasingly likely to develop BCCs on the trunk so that the odds for developing a BCC on the trunk for those who had 5 or more SKs at this body site were 3 times greater (OR 3.3, 95%CI 1.4-7.6) than those without SKs on the trunk. The presence of any solar lentigines on the back was significantly associated with BCCs on the trunk and the association was strongest among those cases who had many solar lentigines (OR 2.5, 95%CI 1.3-4.9, Table 2) but neither freckles on the trunk nor melanocytic nevi on the back were associated with BCCs on the trunk. Similarly, while melanocytic nevi on the arms were not associated with limb BCCs, 5 or more SKs on the limbs were strongly associated (OR 3.7, 95%CI 2.0-7.0, Table 2). Supplementary Table 1 shows associations between each measure of photodamage and BCCs at each anatomic site.

We repeated analyses after exclusion of the 66 participants who had a past history of BCC, most of whom (79%) went on to develop multiple BCCs in the study period. When analyses were based only on those participants (n=335) who experienced their first BCC during the observation period, there was no material difference in results.
Discussion

In this prospective study of 401 people affected by incident BCC in a 16-year period we found that those who developed high numbers of incident BCCs were significantly more likely than those who developed a single BCC to have been diagnosed previously with SKs. There were no significant differences in pigmented traits or self-reported sun exposure histories among BCC cases who developed multiple compared with a single BCC however, in contrast to our study hypothesis. BCCs were more likely to occur on sites that had clinical evidence of photodamage than on sites without. We also showed that people with multiple BCCs are usually affected at more than one site, almost always including the head/neck.

Previous studies have described the predilection for sun-sensitive pigmented traits seen among people affected by BCC compared to those without BCC. Our study extends this work to describe the differences between cases who developed intermediate or high numbers of BCCs compared to those who developed a single BCC in over a decade and a half of follow-up. Complexion type was not associated with the numbers of BCCs people developed, in agreement with a hospital-based British study of 266 BCC cases who found no significant association between the skin’s ability to tan and rate of development of subsequent BCCs.

We next assessed if sun exposure history was able to distinguish between people with single versus multiple BCCs but after prolonged follow-up we found no association with recreational or occupational sun exposure. Nor did we find any
evidence that the number of sunburns, a measure of acute sun damage, was associated with multiple BCCs. Our results again agree with those of the British study, which found no association between individuals’ hours of sun exposure per year prior to their first BCC or number of childhood sunburns and the number of subsequent BCCs. While ultraviolet radiation (UVR) is the main environmental factor in the development of BCCs, current available evidence cannot reliably identify the specific aspects of UVR exposure concerned with the occurrence of BCCs (whether initial or subsequent). This can be attributed partly to the recall error that is inherent in all self-reported estimates of past sun exposure and partly to the self-selection of susceptible people to an indoor lifestyle.

In contrast, an association between objective clinical markers of photodamage and general BCC occurrence was noted and this has been described previously by other investigators. We have now precisely quantified the relationship, in particular the strong associations between total body SK counts and intermediate and high numbers of BCCs, overall and site-specifically. The objective presence of SKs flags a history of chronic sun exposure and removes the error when recall is used to assess the past sun exposure of an individual. Moreover their site-specific prevalence can be regarded as evidence for and personal dosimeters of chronic sun damage to the site affected by SKs, making them useful for quantifying site-specific associations between UVR and BCC. Thus our data indicate that those who develop multiple BCCs have received a greater dose of UVR than people with a single BCC, in general as well as on specific sites, even including the trunk and limbs.
The theory that different causal mechanisms are responsible for the pathogenesis of BCC on different anatomic site was largely based on cross-sectional findings showing that sun-sensitivity and cutaneous sun damage were risk factors for a first BCC on the head/neck, whereas a less sun-sensitive phenotype and a history of sunburns were associated with a first BCC on the trunk\textsuperscript{12,14,15}. It is important to note that these studies did not take into account any subsequent BCCs (and their site) that the participants developed. Meanwhile another study described in broad terms how people with multiple BCCs tended to develop their BCCs on a single site\textsuperscript{16}, presented no evidence about the proportion of people who developed BCC on a single or more than one site. On the other hand a hospital-based Dutch study with a median follow-up time of 3.1-years revealed that 33% of people affected by multiple BCCs were affected across different sites\textsuperscript{9}. In a US study 45% of people affected by multiple BCCs developed BCCs on different sites during 7-years of follow-up\textsuperscript{17}. In the present study, with 16-years of follow-up, 60% of people with multiple occurrences of BCC developed BCCs on more than one anatomic region suggesting a common pathogenic mechanism is shared by BCCs across sites.

Regarding limitations of this study, although our findings did not suggest that sunburns contributed to BCC multiplicity we could not exclude this possibility because of the known poor reproducibility of sunburn history\textsuperscript{27}. Consequently we have not been able to assess if the acute intense pattern of UVR is associated with BCC multiplicity and site. Whilst some participants had a BCC prior to the observation period, the BCC records for that time were incomplete for some participants. We can therefore only be certain about the BCC status of all participants for the 16-year observation period. On repeating our analyses only in
those who did not have previous BCC however, similar results were obtained and thus we believe this has not influenced our findings to any material extent.

In conclusion, we have shown that among people affected by BCC, those who develop intermediate or high numbers of BCCs show evidence of severe sun damage both overall and for BCCs at different sites. *How might our findings be useful as evidence for effective BCC prevention and healthcare?* These findings suggest that control of BCC multiplicity in the population at large is feasible through decreasing cumulative sun exposure, thereby helping to curb the substantial encumbrance that BCC places on health systems serving white populations. Follow-up of BCC patients requires thorough whole body skin examinations, rather than being limited to typically sun-exposed sites or to sites previously affected by BCCs.
Acknowledgements

We thank the Nambour Skin Cancer Study participants and their doctors who assisted in long-term monitoring of skin cancer. Many volunteer helpers from the Nambour community have given their invaluable support to these studies. Our thanks are extended to Queensland Medical Laboratory and Sullivan Nicolaides Pathology for providing pathology reports for all study tumors.

This work was supported by a grant from the National Health and Medical Research Council [grant number 442976]. Naomi Richmond-Sinclair was supported by a Smart State PhD Scholarship, an ANZ Trustees Medical Research in Queensland PhD Scholarship and Queensland Institute of Medical Research PhD Top-Up Scholarship. Rachel Neale is supported by a NHMRC (Aust) Career Development Award.
References


Figures

Figure 1: Anatomic sites of basal cell carcinoma (BCC) among people with single and multiple occurrences of BCC in 1992 to 2007, Queensland, Australia
Table 1: Odds ratios for multiple basal cell carcinomas (BCC) compared to people with a single BCC in 1992 to 2007, according to age, sex, pigmentary traits, sun exposure and cutaneous signs of sun damage in Queensland, Australia

<table>
<thead>
<tr>
<th>Participant characteristics</th>
<th>Distribution of cases (count (%))</th>
<th>Persons with 2 to 3 BCCs</th>
<th>Persons with ≥4 BCCs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n=401)</td>
<td>Single BCC (reference, n=169)</td>
<td>2 to 3 BCCs (n=139)</td>
</tr>
<tr>
<td>Age&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 40 years</td>
<td>54 (13%)</td>
<td>28 (17%)</td>
<td>18 (13%)</td>
</tr>
<tr>
<td>40 to 59 years</td>
<td>203 (51%)</td>
<td>92 (54%)</td>
<td>69 (50%)</td>
</tr>
<tr>
<td>60 years or older</td>
<td>144 (36%)</td>
<td>49 (29%)</td>
<td>52 (37%)</td>
</tr>
<tr>
<td>Sex&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>207 (52%)</td>
<td>100 (59%)</td>
<td>70 (50%)</td>
</tr>
<tr>
<td>Male</td>
<td>194 (48%)</td>
<td>69 (41%)</td>
<td>69 (50%)</td>
</tr>
<tr>
<td>Pigmentation traits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin color&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olive / medium</td>
<td>152 (38%)</td>
<td>66 (39%)</td>
<td>56 (40%)</td>
</tr>
<tr>
<td>Fair</td>
<td>249 (62%)</td>
<td>103 (61%)</td>
<td>83 (60%)</td>
</tr>
<tr>
<td>Skin response to sun exposure&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tan / burn then tan</td>
<td>295 (74%)</td>
<td>125 (74%)</td>
<td>109 (78%)</td>
</tr>
<tr>
<td>Always burn</td>
<td>106 (26%)</td>
<td>44 (26%)</td>
<td>30 (22%)</td>
</tr>
<tr>
<td>Eye color&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dark / light brown</td>
<td>38 (10%)</td>
<td>21 (12%)</td>
<td>10 (7%)</td>
</tr>
<tr>
<td>Hazel / green</td>
<td>165 (41%)</td>
<td>70 (42%)</td>
<td>61 (44%)</td>
</tr>
<tr>
<td>Blue/grey</td>
<td>195 (49%)</td>
<td>77 (46%)</td>
<td>67 (49%)</td>
</tr>
<tr>
<td>Hair color&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black / Dark brown</td>
<td>158 (40%)</td>
<td>69 (41%)</td>
<td>57 (41%)</td>
</tr>
<tr>
<td>Light brown / blonde</td>
<td>203 (51%)</td>
<td>88 (52%)</td>
<td>64 (47%)</td>
</tr>
<tr>
<td>Red / ginger / auburn</td>
<td>37 (9%)</td>
<td>11 (7%)</td>
<td>17 (12%)</td>
</tr>
<tr>
<td>Melanocytic nevi on back&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>52 (15%)</td>
<td>13 (8%)</td>
<td>22 (16%)</td>
</tr>
<tr>
<td>Yes</td>
<td>346 (85%)</td>
<td>155 (92%)</td>
<td>117 (84%)</td>
</tr>
<tr>
<td>Melanocytic nevi on arms&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>238 (60%)</td>
<td>98 (59%)</td>
<td>87 (63%)</td>
</tr>
<tr>
<td>Yes</td>
<td>157 (40%)</td>
<td>68 (41%)</td>
<td>52 (37%)</td>
</tr>
</tbody>
</table>
### Sun exposure

<table>
<thead>
<tr>
<th>Recreation type</th>
<th>Number</th>
<th>Percent</th>
<th>Number</th>
<th>Percent</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mainly indoors</td>
<td>67 (17%)</td>
<td>27 (16%)</td>
<td>24 (17%)</td>
<td>16 (17%)</td>
<td>1.0 Ref</td>
<td>1.0 Ref</td>
<td>0.31, 1.5</td>
<td>0.54 (0.22, 1.4)</td>
</tr>
<tr>
<td>Indoors and outdoors</td>
<td>115 (28%)</td>
<td>52 (31%)</td>
<td>39 (28%)</td>
<td>24 (26%)</td>
<td>0.68 (0.31, 1.5)</td>
<td>1.0 Ref</td>
<td>0.54 (0.22, 1.3)</td>
<td></td>
</tr>
<tr>
<td>Mainly outdoors</td>
<td>219 (55%)</td>
<td>90 (53%)</td>
<td>76 (55%)</td>
<td>53 (57%)</td>
<td>0.63 (0.30, 1.3)</td>
<td>0.54 (0.22, 1.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Occupation type</th>
<th>Number</th>
<th>Percent</th>
<th>Number</th>
<th>Percent</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mainly indoors</td>
<td>153 (38%)</td>
<td>65 (39%)</td>
<td>56 (40%)</td>
<td>32 (34%)</td>
<td>1.0 Ref</td>
<td>1.0 Ref</td>
<td>0.49, 1.5</td>
<td>1.0 (0.55, 2.0)</td>
</tr>
<tr>
<td>Indoors and outdoors</td>
<td>146 (37%)</td>
<td>62 (37%)</td>
<td>50 (36%)</td>
<td>34 (37%)</td>
<td>0.84 (0.49, 1.5)</td>
<td>1.0</td>
<td>0.54 (0.22, 1.3)</td>
<td></td>
</tr>
<tr>
<td>Mainly outdoors</td>
<td>100 (25%)</td>
<td>40 (24%)</td>
<td>33 (24%)</td>
<td>27 (29%)</td>
<td>0.59 (0.30, 1.2)</td>
<td>0.80 (0.38, 1.7)</td>
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</tr>
</tbody>
</table>

### Cutaneous signs of sun damage

#### Acute

<table>
<thead>
<tr>
<th>Number of painful sunburns</th>
<th>Number</th>
<th>Percent</th>
<th>Number</th>
<th>Percent</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>47 (12%)</td>
<td>20 (12%)</td>
<td>18 (13%)</td>
<td>9 (10%)</td>
<td>1.0 Ref</td>
<td>1.0 Ref</td>
<td>0.47, 2.2</td>
<td>1.7 (0.67, 4.4)</td>
</tr>
<tr>
<td>1 to 5</td>
<td>200 (50%)</td>
<td>86 (51%)</td>
<td>70 (50%)</td>
<td>44 (47%)</td>
<td>1.0</td>
<td>0.72 (0.37, 1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 or more</td>
<td>154 (38%)</td>
<td>63 (37%)</td>
<td>51 (37%)</td>
<td>40 (43%)</td>
<td>1.0 (0.43, 2.3)</td>
<td>1.8 (0.66, 4.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Chronic

<table>
<thead>
<tr>
<th>Telangiectasia of the face</th>
<th>Number</th>
<th>Percent</th>
<th>Number</th>
<th>Percent</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>None / mild</td>
<td>217 (54%)</td>
<td>97 (57%)</td>
<td>68 (49%)</td>
<td>52 (56%)</td>
<td>1.0 Ref</td>
<td>1.0 Ref</td>
<td>0.76, 2.3</td>
<td>0.72 (0.37, 1.4)</td>
</tr>
<tr>
<td>Moderate / severe</td>
<td>184 (46%)</td>
<td>72 (43%)</td>
<td>71 (51%)</td>
<td>41 (44%)</td>
<td>1.3 (0.76, 2.3)</td>
<td>0.72 (0.37, 1.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Solar elastosis of the neck</th>
<th>Number</th>
<th>Percent</th>
<th>Number</th>
<th>Percent</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>None / mild</td>
<td>194 (48%)</td>
<td>91 (54%)</td>
<td>58 (42%)</td>
<td>45 (48%)</td>
<td>1.0 Ref</td>
<td>1.0 Ref</td>
<td>0.90, 2.6</td>
<td>0.86 (0.47, 1.6)</td>
</tr>
<tr>
<td>Moderate / severe</td>
<td>207 (52%)</td>
<td>78 (46%)</td>
<td>81 (58%)</td>
<td>48 (52%)</td>
<td>1.5 (0.90, 2.6)</td>
<td>0.86 (0.47, 1.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Solar Keratoses</th>
<th>Number</th>
<th>Percent</th>
<th>Number</th>
<th>Percent</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>58 (15%)</td>
<td>37 (22%)</td>
<td>17 (12%)</td>
<td>4 (4%)</td>
<td>1.0 Ref</td>
<td>1.0 Ref</td>
<td>0.69, 3.0</td>
<td>3.9 (1.2, 12.5)</td>
</tr>
<tr>
<td>1 to 4</td>
<td>105 (26%)</td>
<td>47 (28%)</td>
<td>34 (25%)</td>
<td>24 (26%)</td>
<td>1.4 (0.69, 3.0)</td>
<td>3.9 (1.2, 12.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 or more</td>
<td>238 (59%)</td>
<td>85 (50%)</td>
<td>88 (63%)</td>
<td>65 (70%)</td>
<td>1.9 (0.92, 3.8)</td>
<td>4.3 (1.4, 13.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 CI, confidence interval;

2 Estimates were derived from a model that contained age, sex, randomised sunscreen treatment, self-reported skin response to acute sun exposure, sunscreen use since the trial and skin response to sun exposure, eye color, occupation type and number of lifetime sunburns;

3 The model was the same as in 2 but also contained hair color, recreation type, telangiectasia of the face and elastosis of the neck;

4 The model included age, sex, randomised sunscreen treatment, self-reported skin response to acute sun exposure and total number of solar keratoses or nevi where appropriate.

Table 2: Odds ratios\(^1\) for anatomic site of basal cell carcinoma (BCC) according to
cutaneous signs of sun damage of skin at the same site among people affected 1992 to 2007, in Queensland, Australia

<table>
<thead>
<tr>
<th>Cutaneous signs of sun damage</th>
<th>Distribution of BCCs (count (%))</th>
<th>Odds ratios</th>
<th>95% CI²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Head/neck</strong></td>
<td><strong>Trunk or limbs (n=345)³</strong></td>
<td><strong>Head/neck (n=856)⁴</strong></td>
<td><strong>Head/neck</strong></td>
</tr>
<tr>
<td>Telangiectasia of face</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>25 (7%)</td>
<td>22 (3%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Mild / moderate / severe</td>
<td>320 (93%)</td>
<td>834 (97%)</td>
<td>2.1</td>
</tr>
<tr>
<td>Solar lentigines on face</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>79 (23%)</td>
<td>161 (19%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Some</td>
<td>213 (62%)</td>
<td>527 (61%)</td>
<td>1.2</td>
</tr>
<tr>
<td>Many</td>
<td>53 (15%)</td>
<td>168 (20%)</td>
<td>1.8</td>
</tr>
<tr>
<td>Solar elastosis of neck</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>16 (5%)</td>
<td>13 (2%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Mild / moderate / severe</td>
<td>329 (95%)</td>
<td>843 (98%)</td>
<td>1.7</td>
</tr>
<tr>
<td>Solar Keratoses on face</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>54 (16%)</td>
<td>64 (8%)</td>
<td>1.0</td>
</tr>
<tr>
<td>1 to 4</td>
<td>118 (34%)</td>
<td>238 (28%)</td>
<td>1.4</td>
</tr>
<tr>
<td>5 or more</td>
<td>173 (50%)</td>
<td>554 (64%)</td>
<td>2.0</td>
</tr>
<tr>
<td>Trunk</td>
<td><strong>Head/neck or limbs (n=574)⁵</strong></td>
<td><strong>Trunk (n=627)⁶</strong></td>
<td><strong>Trunk</strong></td>
</tr>
<tr>
<td>Freckles on trunk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>89 (16%)</td>
<td>79 (13%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Some</td>
<td>184 (32%)</td>
<td>247 (39%)</td>
<td>1.6</td>
</tr>
<tr>
<td>Many</td>
<td>300 (52%)</td>
<td>297 (48%)</td>
<td>1.5</td>
</tr>
<tr>
<td>Solar lentigines on back</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>182 (32%)</td>
<td>119 (19%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Some</td>
<td>258 (45%)</td>
<td>309 (50%)</td>
<td>1.7</td>
</tr>
<tr>
<td>Many</td>
<td>132 (23%)</td>
<td>193 (31%)</td>
<td>2.5</td>
</tr>
<tr>
<td>Melanocytic nevi on back</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>78 (14%)</td>
<td>111 (18%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Some</td>
<td>417 (73%)</td>
<td>411 (66%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Many</td>
<td>77 (13%)</td>
<td>101 (16%)</td>
<td>1.4</td>
</tr>
<tr>
<td>Solar keratoses on trunk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>413 (72%)</td>
<td>317 (51%)</td>
<td>1.0</td>
</tr>
<tr>
<td>1 to 4</td>
<td>135 (24%)</td>
<td>206 (33%)</td>
<td>1.6</td>
</tr>
<tr>
<td>5 or more</td>
<td>26 (4%)</td>
<td>104 (16%)</td>
<td>3.3</td>
</tr>
<tr>
<td>Limbs</td>
<td>Head/neck or trunk (n=721)</td>
<td>Limbs (n=480)</td>
<td>Limbs</td>
</tr>
<tr>
<td>-------</td>
<td>---------------------------</td>
<td>---------------</td>
<td>-------</td>
</tr>
<tr>
<td>Nevi on arms</td>
<td>No</td>
<td>409 (58%)</td>
<td>350 (75%)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>301 (42%)</td>
<td>114 (25%)</td>
</tr>
<tr>
<td>Solar Keratoses on limbs</td>
<td>None</td>
<td>217 (30%)</td>
<td>58 (12%)</td>
</tr>
<tr>
<td></td>
<td>1 to 4</td>
<td>200 (28%)</td>
<td>55 (12%)</td>
</tr>
<tr>
<td></td>
<td>5 or more</td>
<td>304 (42%)</td>
<td>367 (76%)</td>
</tr>
</tbody>
</table>

1 Adjusted for age, sex, skin color and randomised sunscreen treatment;
2 CI, confidence interval;
3 Reference group: BCCs that developed on either the trunk or limbs;
4 BCCs that developed on the head/neck only;
5 Reference group: BCCs that developed on either the head/neck or limbs;
6 BCCs that developed on the trunk;
7 Reference group: BCCs that developed on either the head/neck or trunk;
8 BCCs that developed on the limbs.
Anatomic site combinations affected by basal cell carcinoma

- Head/neck only: 47%
- Trunk only: 15%
- Head/neck and trunk: 29%
- Limbs only: 21%
- Head/neck, trunk and limbs: 24%
- Head/neck and limbs: 7%
- Trunk and limbs: 1%

Affected groups:
- Single BCC (n=169)
- 2-3 BCCs (n=139)
- >4 BCCs (n=93)

% of people affected relative to their affected group

317x179mm (96 x 96 DPI)
CHAPTER 5

OCCURRENCE AND DETERMINANTS OF BASAL CELL CARCINOMA BY HISTOLOGICAL SUBTYPE IN AN AUSTRALIAN COMMUNITY COHORT
5.1 Introduction

This results chapter comprises a manuscript that will soon be submitted to an international peer-reviewed journal, and as such is presented here in a general format required for manuscript submission. It directly addresses research questions R5 and R6 (see section 1.7): what are the common histological growth patterns of basal cell carcinoma in a high risk Australian population? and do nodular and superficial BCCs have the same association to risk factors (age, sex, pigmentary traits, sun exposure, sun dose) when compared to people unaffected by BCC?

5.2 Contribution of candidate

I conceived and designed the investigation with advice from Prof Adèle Green and Dr Jolieke van der Pols. I developed new variables to capture the number of times a person had been affected by BCC during the observation period and all of the time-dependent variables that captured each person’s sun exposure history and degree of photodamage. The remaining variables were available in the existing datasets. I requested pathology reports from the Queensland pathology laboratories for those lesions that did not have data available for the specific histologic growth patterns and assisted with the data entry for this information. I performed the data analyses and drafted the manuscript.

5.3 Acknowledgement of the contribution of others

All the data included in the following manuscript were collected as part of the Nambour Skin Cancer Study. The Nambour Skin Cancer Follow-up Study was conceived and designed by the chief investigators, namely, Prof Adèle Green and Prof. Gail Williams. Prof H.Konrad Muller assisted with the classification of the BCC growth patterns and the editing of the manuscript. Dr Jolieke van der Pols and Prof Adèle Green contributed to the
interpretation of the results and assisted with the editing and drafting of the manuscript.

Principal Supervisor Confirmation

The authors listed above have certified that:

1. they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
2. they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
3. there are no other authors of the publication according to these criteria;
4. potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit, and
5. they agree to the use of the publication in the student’s thesis and its publication on the Australasian Digital Thesis database consistent with any limitations set by publisher requirements.

I have sighted email correspondence from all Co-authors confirming their certifying authorship.

Adèle C Green

Name       Signature                        Date

5.4 Manuscript: Occurrence and determinants of basal cell carcinoma by histological subtype in an Australian community cohort
Title  Occurrence and determinants of basal cell carcinoma by histological subtype in an Australian community cohort

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Word count: 2537 (excludes abstract, acknowledgements, reference list, figures and tables)

Number of tables:  1  Number of figures:  2  Number of references:  26
Abstract

Background The pleomorphism of basal cell carcinoma (BCC) is well-known but the relative frequencies and causes of different growth patterns are not.

Objective Describe frequencies of growth patterns and quantify the associations between pigmented traits and sun exposure and nodular and superficial BCCs.

Method In a community-based cohort in Queensland, Australia, we prospectively recorded growth patterns and sites of all confirmed BCCs (1992 to 2007). Risks of nodular and superficial BCCs in relation to baseline phenotype and sun exposure were estimated using logistic regression.

Results In 16-years, 401 of the cohort of 1339 (average age 49 at baseline) developed 1202 BCCs. 792 (77%) had a single growth pattern and 235 (23%) were mixed. Among all BCCs the nodular followed by the superficial growth patterns were commonest. In general, compared to people unaffected, risks of nodular and superficial BCCs were significantly raised among those older than 50, males, those with light eye color or multiple past sunburns. Risk of nodular and superficial BCCs on the head was raised if 5 or more solar keratoses were present on the face (ORs 1.8 and 4.5 respectively) and similarly on the trunk in the presence of multiple solar keratoses on the trunk (ORs 4.2 and 2.2 respectively).

Limitations The predominant growth pattern was not available for BCCs with mixed composition.

Conclusion We conclude that nodular and superficial BCCs have similar associations with severely sun damaged skin whatever the site, suggesting that actual BCC growth patterns are determined by local tissue factors rather than degree of sun exposure.
Capsule summary

- Among people affected by BCCs nearly 40% develop BCCs with mixed histologic composition.
- BCCs of nodular and superficial growth patterns have similar etiologies with regard to the affected persons’ sun exposure histories and their clinical signs of severe sun damage.
- The observed growth patterns of BCCs are probably determined by local tissue factors rather than external exposure factors.

Abbreviations

BCC, basal cell carcinoma
OR, odds ratio
CI, confidence interval
SK, solar keratosis
Introduction

Basal cell carcinomas (BCC) are distinct skin cancers occurring with high frequency and highly varied histologic presentations. At least 20 BCC subtypes have been defined and mixed composition is not unusual.

The well-described histological morphologies include the nodular, superficial and morpheaic/infiltrative subtypes. The nodular growth pattern is the most common (accounting for up to 81% of BCCs) and BCCs of this type tend to occur on the head and neck. This is the anatomic site with the highest opportunity for sun exposure and also the site most frequently treated for BCC overall. Superficial BCCs are the second most common and occur predominantly on the trunk, the site second most commonly treated for BCC. These collective findings have led to the hypothesis that BCC histological subtypes have different etiologies. The majority of studies that have supported this hypothesis however have been based on assorted large series of retrospectively collected pathology reports. Furthermore the only study that assessed risk factors for nodular and superficial BCCs separately did not account for anatomic site of occurrence. Hence it remains unclear if risk factors for BCCs of certain subtypes are determined by their anatomic sites of occurrence, the sun exposure histories of the host, or some other factors. The epidemiology of BCCs of mixed histologic composition remains unknown.

We monitored the occurrence of BCC according to growth patterns among participants in a community-based skin cancer study in subtropical Queensland, Australia during the period 1992 to 2007. We further conducted a detailed assessment of personal and environmental factors associated with the development of the main histological growth patterns of BCC. We hypothesised that BCCs of different histological subtypes have similar rather than different etiologies with regard to sun exposure histories of affected persons.
Materials and methods

The Nambour Skin Cancer Study

Study participants were originally randomly selected in 1986 from the electoral register of all adult residents of the subtropical township of Nambour in Queensland, Australia (latitude 26°S) for a baseline study of skin cancer. 2095 people (70%) took part and were shown to be a representative sample of the community with regard to risk factors for skin cancer. Of these, 1621 (77%) participated in a field trial between 1992 and 1996 to assess sunscreen application and betacarotene supplementation in the prevention of skin cancer and full details have been published previously. In 1996, participants were invited to take part in a further follow-up study of skin cancer and provided consent to have subsequently diagnosed skin cancers notified to the investigators by regional pathology laboratories in Queensland, allowing 100% ascertainment of all histologically confirmed BCCs. No participants were immuno-compromised, and none had nevoid basal cell carcinoma syndrome. Follow-up for skin cancers continued to the end of 2007. Ethical approval was obtained from the ethics committee of the Queensland Institute of Medical Research.

Basal cell carcinomas

People who experienced a new histologically-confirmed BCC during the study period, 1992 to 2007, were considered cases. Investigators abstracted details of histologic subtype from pathology reports. If more than one growth pattern was described all were recorded. The BCC histological subclassification system proposed by the World Health Organisation was applied for those tumors with a single growth pattern. Because the same BCC may be histologically confirmed twice, at initial biopsy/excision and again if re-excised, all records of apparently multiple BCCs verified within a 6-month period in the same person and on the same anatomic site were
cross-checked to identify duplicate reports. Recurrent BCCs diagnosed at the sites of earlier primary lesions were excluded.

*Pigmentary traits, sun exposure and photodamage*

Participants’ head, neck, and trunk were examined in 1986, 1992, 1994 and 1996 by dermatologists who documented the number and sites of solar keratoses. All participants completed a baseline standard questionnaire about pigmentary traits (skin and eye color) and sun-exposure habits (occupation and number of lifetime painful sunburns), which was updated during the trial and additional information obtained about participants’ skin responses to acute sun exposure. From 1997, participants reported their sunscreen use each year and based on their responses were classified as regular or irregular sunscreen users.

*Statistical analysis*

Repeated-measures binomial logistic regression was used to assess the associations between personal factors and BCCs of nodular and of superficial histological subtypes (there were insufficient numbers of the less common subtypes), taking participants unaffected by BCC during the study period as the reference group. The repeated-measures analyses accounted for the intra-person correlation when people had multiple BCCs. Differences between nodular and superficial BCCs were formally tested by a case-case comparison of nodular and superficial BCC cases. Each exposure variable was treated categorically to estimate the odds ratio (OR) with 95% confidence intervals. Analyses were stratified by anatomic site to account for differences in the proportion of BCCs of the nodular or superficial growth pattern that occurred by site and all analyses were adjusted for age, sex, and randomised sunscreen treatment during the trial. Only a person’s sun exposure and photodamage recorded prior to the date of diagnosis of BCC were considered. Statistical analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina) and SUDAAN 10 (RTI Institute, Research Triangle Park, North Carolina).
Results

Study population

1339 participants had complete follow-up until the end of 2007. At the start of follow-up in 1992 their mean age was 49 years, and 56% were female. Of these, 401 (207 women) were diagnosed with a combined total of 1202 histologically-confirmed BCCs. 169 people developed one BCC only (42%, including 100 women) and 232 people developed more than one BCC (58%, including 107 women).

Prevalence of single and mixed histological composition

Histological growth patterns were available for 1027 (85%) of the BCCs. Pathology reports were unavailable for 5 BCCs and growth patterns were not reported for 170 BCCs. BCCs with unknown growth patterns were similar to BCCs with known growth patterns in terms of age at diagnosis, sex, site of occurrence and skin color, however, they were more likely to have been diagnosed in earlier study years (prior to 1997, 63% and 34% respectively (p=<0.001)). Among the BCCs with known growth patterns, 792 (77%) BCCs from 329 (82%) people had a single growth pattern, while 235 (23%) BCCs from 153 (38%) people had mixed composition, with up to three different growth patterns in a single BCC. 212 (21%) had two different growth patterns and 23 (2%) had three different growth patterns. In this series of BCCs 19 different growth patterns were described. There was little difference in sex and age of persons with single or mixed composition tumours.

Among the 792 BCCs with a single growth pattern the nodular type was the most common (403, 51%) followed by superficial (284, 36%), morpheic (48, 6%) and then micronodular (18, 27%) BCCs (Figure 1). Among 235 BCCs with mixed histological composition, the nodular pattern was present in 200 (85%) BCCs of which 104 (44%) also showed morpheic growth patterns,
while 56 (24%) also showed a superficial growth pattern component (Figure 1).

One versus multiple basal cell carcinomas

Among the 146 people affected once by BCC, 111 (76%) had a BCC of a single growth pattern. Among the 226 people affected by multiple BCCs, 218 (96%) had at least one BCC of a single growth pattern (total 681 BCCs with a single pattern) and 117 (52%) were diagnosed with at least one BCC of two or more growth patterns (total 200 with mixed pattern). The proportions of BCCs with single and mixed histological composition were similar among people affected by one or multiple BCCs (p=0.7, Figure 1).

Anatomic distribution

Of the 533 BCCs on the head and neck of known growth pattern, 375 (71%) had a single growth pattern, lower than for BCCs on the trunk (237, 86%) and limbs (177, 83%, Figure 2). As a corollary more BCCs on the head and neck were of mixed composition (p=<0.001). The most common growth pattern in head and neck BCCs was nodular and it was exclusively present in almost half (243, 46%). In contrast BCCs on trunk (119, 43%) and limbs (99, 47%) the superficial growth pattern predominated (Figure 2). Among BCCs with mixed histological composition, nodular remained the dominant pattern on all three anatomic sites.

With regard to anatomic subsites on the head and neck (forehead, temples, ears, eyes, nose, cheek, perioral, chin, jaw, scalp, and neck) the proportion of BCCs with a single growth pattern was similar across subsites (around 30%). Further, among head and neck BCCs with a single growth pattern the highest proportion of nodular BCCs occurred in the periocular region (83%), whereas the cheek and perioral, and neck subsites had the greatest proportions of superficial BCC (24% and 32% respectively). Varying
proportions of BCCs of the nodular, superficial and morpheic growth patterns occurred at each subsite (p=0.06).

Determinants of the nodular and superficial growth patterns

Head and neck

People aged 50 years or older were more likely to have a nodular or superficial BCC on the head and neck than those aged under 50.

The age association was strongest for nodular BCCs: the odds of having a nodular BCC among those aged 50 years or older at the start of observation were 4 times higher (OR=4.4, 95%CI 3.0-6.4, Table 1) compared to those who were younger. Nodular BCCs were more likely to occur among males than females (OR=2.2, 95%CI 1.6-3.3). Compared to people with darker pigmentation traits, those with lighter, sun-sensitive phenotypes were generally at increased risk of both nodular and superficial BCCs although the magnitude and significance of individual associations varied (Table 1). A history of 5 or more painful sunburns was strongly associated with nodular BCC (OR=3.2, 95%CI 1.8-5.7, (Table 1) but not significantly with superficial BCC.

Although we found no association between reported occupational sun exposure and the diagnosis of BCCs of either growth pattern, strong associations with high numbers of facial solar keratoses were evident for BCCs of the nodular (OR=1.8, 95%CI 1.2-2.7) and superficial (OR=4.5, 95%CI 2.1-9.7, Table 1) growth patterns compared to those with no solar keratoses.

Trunk

Overall, the associations between each of the risk factors and nodular and superficial BCCs on the trunk were similar to those for BCC on the head and
neck apart from a lack of association between sun-sensitive skin type and BCCs on the trunk of either subtype. Strong associations with increasing truncal solar keratoses counts were particularly evident for both BCC subtypes on the trunk (Table 1).

Differences between nodular and superficial BCCs

Among BCCs on the head and neck the only significant difference between nodular and superficial BCCs was that people aged 50 years or older and males were more likely to develop a nodular BCC (data not shown). This was not true for truncal BCCs. With regard to the associations with pigmentary traits, sun exposure and solar keratoses there were no significant differences between the two growth patterns at either site.

Discussion

In this prospective community-based study with 401 people affected by one or more BCCs, we found that while most BCCs had a single histological growth pattern, mixed histological composition was seen in around a quarter of all new BCCs in the 16-year follow-up period. When compared to people unaffected by BCC, there were no consistent and significant differences between risk factors for nodular and superficial BCCs with regard to pigmentary traits, self-reported sun exposure history or evidence of severe sun damage.

It has been suggested that superficial and nodular BCCs vary in their causal relationship to sunlight. Whilst previous studies have found superficial BCCs to be diagnosed at an earlier age and more often on the trunk when compared to nodular BCCs, these studies tended to be cross-sectional data or based on persons’ first BCCs only. The only previous study to assess the association between patient characteristics and BCC histology did not account for anatomic sites of occurrence, and hence it was unclear if the risk factors they identified for BCCs, namely solar keratoses and past sun burns,
were determined by the anatomic site rather than the sun exposure history per se. To overcome this problem we stratified by anatomic site in order to account for the large difference in opportunity for sun exposure on the head and neck and the trunk. It was then clear in our large community series of BCCs that there was no material difference between BCCs of the nodular and superficial growth patterns with regard to complexion, personal sun exposure history or clinical evidence of photoaging. This was in line with our study hypothesis. That is, BCCs of different histological growth patterns appeared to have similar etiologies which suggests that the growth patterns of BCCs are determined by their micro-environment (the skin at the anatomic site) influencing a multipotent cell of origin \(^{20, 21}\) rather than the external environment (sun exposure history).

Few previous studies have reported the details of occurrence of mixed histological composition among BCCs \(^3, 6, 7\); some have reported the predominant growth pattern only \(^22\). In 1039 consecutive BCCs collected from American Hospital archives, up to 38% had evidence of mixed histology \(^23\), however, in another American case series 76% of 175 BCCs exhibited mixed histology (though the selection method for BCCs was not clear) \(^24\). We have confirmed that mixed histological composition among BCCs is not uncommon. It seems likely that this diversity in growth patterns reflects the BCC’s origin in a multipotent epithelial stem cell \(^20, 25\).

Our findings also showed that the nodular growth pattern is the most common among BCCs (including among those of mixed composition), followed by the superficial growth pattern \(^7, 9\). This is consistent with the findings of a previous study that reported the nodular pattern was predominant in nearly 50% of BCC with mixed composition \(^24\) and with those of another that documented only mixed compositions that demonstrated the nodular pattern \(^7\). On the other hand our finding that histological growth patterns (and single and mixed compositions) occur in similar proportions among people who develop one or multiple BCCs does not accord with that of a previous study which found that people affected by multiple BCCs tend
to have had superficial rather than nodular tumours\textsuperscript{26}. This may be because the present study is based on longitudinal data supported by a virtually complete skin cancer history for each participant rather than a highly selected cross-sectional sample of the previous series\textsuperscript{26}.

Regarding limitations of the present study, we considered that the rate of reporting of mixed composition BCCs may have changed with time (for example, more mixed BCCs may have been diagnosed in recent study years compared to earlier study years) but this was not true in our dataset. Also we were not able to classify our BCCs with mixed histology according to the World Health Organisation’s classification system because the predominant growth pattern for those BCCs was not available.

In conclusion, we have shown that BCCs of nodular and superficial growth patterns have similar etiologies with regard to affected persons’ sun exposure histories and their clinical signs of severe sun damage. These findings suggest that the observed growth patterns of BCCs are determined by local tissue factors rather than external exposure factors.

\textbf{Acknowledgements}

This work was supported by a grant from the National Health and Medical Research Council [grant number 442976]. Naomi Richmond-Sinclair was supported by a Smart State PhD Scholarship, an ANZ Trustees Medical Research in Queensland PhD Scholarship and Queensland Institute of Medical Research PhD Top-Up Scholarship.

We thank the Nambour Skin Cancer Study participants and their doctors who assisted in long-term monitoring of skin cancer. Many volunteer helpers from the Nambour community have given their invaluable support to these studies. Our thanks are extended to Queensland Medical Laboratory and Sullivan Nicolaides Pathology for providing pathology reports for all study tumors.
References
Figure 1  Histological growth patterns of all basal cell carcinomas (BCC) according to people having a single BCC or multiple BCCs in Queensland, Australia 1992-2007.

*Other* includes microdudular for BCCs with a single histological growth pattern
Figure 2  Histological growth patterns of all basal cell carcinomas (BCC) according to anatomic site of development in Queensland, Australia 1992-2007.

*‘Other’ includes microdudular for BCCs with a single histological growth pattern
Table 1: Odds ratios for persons affected by nodular and superficial growth patterns of basal cell carcinoma (BCC) compared to people unaffected by BCC (1992-2007), Queensland, Australia.

<table>
<thead>
<tr>
<th>Participant Characteristics</th>
<th>Distribution of participants (count (%))</th>
<th>Head and neck</th>
<th>Trunk</th>
<th>Head and neck</th>
<th>Trunk</th>
<th>95% CI</th>
<th>Odds ratios</th>
<th>95% CI</th>
<th>Odds ratios</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Age</td>
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<tr>
<td>Less than 50 years</td>
<td>575 (61%)</td>
<td>58 (24%)</td>
<td>25 (38%)</td>
<td>31 (33%)</td>
<td>41 (34%)</td>
<td>1.0</td>
<td>Ref</td>
<td>1.0</td>
<td>Ref</td>
<td>1.0</td>
</tr>
<tr>
<td>50 years or older</td>
<td>363 (39%)</td>
<td>185 (76%)</td>
<td>40 (62%)</td>
<td>62 (67%)</td>
<td>78 (66%)</td>
<td>4.4</td>
<td>(3.0, 6.4)</td>
<td>2.1</td>
<td>(1.2, 3.8)</td>
<td>2.3</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Female</td>
<td>542 (58%)</td>
<td>88 (36%)</td>
<td>32 (49%)</td>
<td>37 (40%)</td>
<td>45 (38%)</td>
<td>1.0</td>
<td>Ref</td>
<td>1.0</td>
<td>Ref</td>
<td>1.0</td>
</tr>
<tr>
<td>Male</td>
<td>396 (42%)</td>
<td>155 (64%)</td>
<td>33 (51%)</td>
<td>56 (60%)</td>
<td>74 (62%)</td>
<td>2.2</td>
<td>(1.6, 3.3)</td>
<td>1.2</td>
<td>(0.65, 2.2)</td>
<td>1.9</td>
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<tr>
<td>Pigmentation traits</td>
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<td></td>
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<td></td>
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<tr>
<td>Skin color</td>
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<tr>
<td>Olive / medium</td>
<td>447 (48%)</td>
<td>83 (34%)</td>
<td>14 (22%)</td>
<td>38 (41%)</td>
<td>40 (34%)</td>
<td>1.0</td>
<td>Ref</td>
<td>1.0</td>
<td>Ref</td>
<td>1.0</td>
</tr>
<tr>
<td>Fair</td>
<td>491 (52%)</td>
<td>160 (66%)</td>
<td>51 (78%)</td>
<td>55 (59%)</td>
<td>79 (66%)</td>
<td>1.4</td>
<td>(0.9, 2.1)</td>
<td>2.7</td>
<td>(1.2, 6.0)</td>
<td>0.98</td>
</tr>
<tr>
<td>Skin response to sun</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Tan / burn then tan</td>
<td>769 (82%)</td>
<td>162 (67%)</td>
<td>43 (66%)</td>
<td>67 (72%)</td>
<td>80 (67%)</td>
<td>1.0</td>
<td>Ref</td>
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<td>Ref</td>
<td>1.0</td>
</tr>
<tr>
<td>Always burn</td>
<td>169 (18%)</td>
<td>81 (33%)</td>
<td>22 (34%)</td>
<td>26 (28%)</td>
<td>39 (33%)</td>
<td>1.8</td>
<td>(1.2, 2.8)</td>
<td>1.8</td>
<td>(0.88, 3.9)</td>
<td>1.6</td>
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<tr>
<td>Eye color</td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Dark / light brown</td>
<td>199 (21%)</td>
<td>16 (7%)</td>
<td>4 (6%)</td>
<td>7 (8%)</td>
<td>7 (6%)</td>
<td>1.0</td>
<td>Ref</td>
<td>1.0</td>
<td>Ref</td>
<td>1.0</td>
</tr>
<tr>
<td>Hazel / green</td>
<td>345 (37%)</td>
<td>88 (36%)</td>
<td>22 (35%)</td>
<td>30 (32%)</td>
<td>55 (46%)</td>
<td>3.1</td>
<td>(1.6, 6.1)</td>
<td>3.1</td>
<td>(0.90, 10.9)</td>
<td>2.0</td>
</tr>
<tr>
<td>Sun exposure</td>
<td>Blue/grey</td>
<td>386 (42%)</td>
<td>137 (57%)</td>
<td>38 (59%)</td>
<td>56 (60%)</td>
<td>57 (48%)</td>
<td>3.5 (1.8, 6.7)</td>
<td>3.9 (1.1, 7.4)</td>
<td>3.1 (1.3, 7.4)</td>
<td>3.1 (1.2, 8.0)</td>
</tr>
<tr>
<td>Occupation type</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mainly indoors</td>
<td>412 (44%)</td>
<td>81 (33%)</td>
<td>26 (40%)</td>
<td>37 (40%)</td>
<td>42 (35%)</td>
<td>1.0 Ref</td>
<td>1.0 Ref</td>
<td>1.0 Ref</td>
<td>1.0 Ref</td>
<td></td>
</tr>
<tr>
<td>Indoors</td>
<td>327 (35%)</td>
<td>79 (33%)</td>
<td>20 (31%)</td>
<td>33 (35%)</td>
<td>47 (40%)</td>
<td>1.1 (0.71, 1.8)</td>
<td>0.95 (0.44, 2.0)</td>
<td>0.90 (0.49, 1.7)</td>
<td>0.90 (0.51, 1.6)</td>
<td></td>
</tr>
<tr>
<td>Mainly outdoors</td>
<td>199 (21%)</td>
<td>82 (34%)</td>
<td>19 (29%)</td>
<td>23 (25%)</td>
<td>30 (25%)</td>
<td>1.4 (0.82, 2.2)</td>
<td>1.2 (0.51, 2.8)</td>
<td>0.95 (0.45, 1.9)</td>
<td>0.67 (0.34, 1.3)</td>
<td></td>
</tr>
<tr>
<td>Number of painful sunburns</td>
<td>None</td>
<td>139 (16%)</td>
<td>31 (13%)</td>
<td>13 (20%)</td>
<td>6 (6%)</td>
<td>13 (11%)</td>
<td>1.0 Ref</td>
<td>1.0 Ref</td>
<td>1.0 Ref</td>
<td></td>
</tr>
<tr>
<td>1 to 5</td>
<td>506 (54%)</td>
<td>111 (46%)</td>
<td>28 (43%)</td>
<td>38 (41%)</td>
<td>60 (50%)</td>
<td>1.4 (0.84, 2.4)</td>
<td>1.0 (0.45, 2.3)</td>
<td>2.4 (0.95, 6.2)</td>
<td>2.0 (0.85, 4.6)</td>
<td></td>
</tr>
<tr>
<td>6 or more</td>
<td>292 (31%)</td>
<td>101 (41%)</td>
<td>24 (37%)</td>
<td>49 (53%)</td>
<td>46 (39%)</td>
<td>3.2 (1.8, 5.7)</td>
<td>1.9 (0.74, 4.9)</td>
<td>6.0 (2.3, 15.8)</td>
<td>3.4 (1.4, 8.5)</td>
<td></td>
</tr>
<tr>
<td>Skin changes</td>
<td>Solar Keratoses on face</td>
<td>None/1 to 4</td>
<td>716 (76%)</td>
<td>90 (37%)</td>
<td>25 (39%)</td>
<td>n/a</td>
<td>1.0 Ref</td>
<td>1.0 Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 or more</td>
<td>222 (34%)</td>
<td>153 (63%)</td>
<td>40 (61%)</td>
<td>n/a</td>
<td>1.8 (1.2, 2.7)</td>
<td>4.5 (2.1, 9.7)</td>
<td>n/a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solar Keratoses on trunk</td>
<td>None</td>
<td>837 (89%)</td>
<td>50 (54%)</td>
<td>69 (58%)</td>
<td>n/a</td>
<td>1.0 Ref</td>
<td>1.0 Ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 to 4</td>
<td>83 (9%)</td>
<td>n/a</td>
<td>27 (29%)</td>
<td>38 (32%)</td>
<td>n/a</td>
<td>2.7 (1.4, 5.5)</td>
<td>2.1 (1.1, 4.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 or more</td>
<td>18 (2%)</td>
<td>16 (17%)</td>
<td>12 (10%)</td>
<td>4.2 (1.5, 11.9)</td>
<td>2.2 (1.1, 4.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 CI, confidence interval;
2 BCCs of the nodular growth pattern only, occurring on the head and neck or the trunk as indicated;
3 BCCs of the superficial growth pattern only, occurring on the head and neck or the trunk as indicated;
4 Estimates were derived from a multivariable model that contained age, sex, randomised sunscreen treatment and self-reported skin response to acute sun exposure in addition to the variable of interest;
5 The model used was the same as 4 but also included a term for occupation;
6 This variable was collapsed into two categories because very few people with facial superficial BCCs had no solar keratoses on the face.
CHAPTER 6

BASAL CELL CARCINOMA AND CUMULATIVE SUN EXPOSURE: AN AUSTRALIAN LONGITUDINAL COMMUNITY-BASED STUDY
6.1 Introduction

This results chapter comprises a manuscript that has been submitted for publication to the *Archives of Dermatology* and as such is presented here in the format required for manuscript submission. This manuscript was first submitted on December 21 2009 and has subsequently been resubmitted with revisions and is awaiting editorial decision. It directly addresses research question R7 (see section 1.7): To what extent do BCCs develop on people who have histological evidence of chronic cutaneous sun damage or other clinical signs of actinic skin damage?

6.2 Contribution of the candidate

I conceived and designed the investigation with advice from Prof Adèle Green and Dr Jolieke van der Pols. I developed new variables to capture the number of times a person had been affected by BCC during the observation period and variables concerning the histology growth patterns of the BCCs. I derived all time-dependent variables that captured each person’s sun exposure history. The remaining variables were available in the existing datasets. I assisted with the physical selection of individual tissue slides that were to be stained and oversaw the handling of the slides. I performed the data analyses and drafted the manuscript.

6.3 Acknowledgement of the contribution of others

All the data included in the following manuscript were collected as part of the Nambour Skin Cancer Study. The Nambour Skin Cancer Study was originally conceived and designed by the Nambour Skin Cancer Study investigators, namely, Prof Adèle Green and Prof Gail Williams. Prof H.Konrad Muller performed the grading of each tissue section for the degree of solar elastosis (see Appendix 4) and the editing of the manuscript. Dr Jolieke van der Pols and Prof Adèle Green contributed to the interpretation of the results and assisted with the editing and drafting of the manuscript.

Principal Supervisor Confirmation
The authors listed above have certified that:

1. they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
2. they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
3. there are no other authors of the publication according to these criteria;
4. potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit, and
5. they agree to the use of the publication in the student's thesis and its publication on the Australasian Digital Thesis database consistent with any limitations set by publisher requirements.

I have sighted email correspondence from all Co-authors confirming their certifying authorship.

Adèle C Green

Name Signature Date

6.4 Manuscript: Basal cell carcinoma and cumulative sun exposure: an Australian longitudinal community-based study
Title

Basal cell carcinoma and measures of cumulative sun exposure: an Australian longitudinal community–based study

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Keywords (MeSH terms)
Basal cell carcinoma, Australia, prospective studies, sunlight, skin aging

Abbreviations
BCC, basal cell carcinoma; CI, confidence interval; OR, odds ratio
Author Contributions:

Naomi Richmond-Sinclair, Dr Jolieke van der Pols, Prof H. Konrad Muller and Prof Adele Green had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Naomi Richmond-Sinclair, Jolieke van der Pols and Adele Green. Acquisition of data: Naomi Richmond-Sinclair, H. Konrad Muller and Adele Green. Analysis and interpretation of data: Naomi Richmond-Sinclair, Jolieke van der Pols, H. Konrad Muller, Adele Green. Drafting of the manuscript: Naomi Richmond-Sinclair, Jolieke van der Pols and Adele Green. Critical revision of the manuscript for important intellectual content: Naomi Richmond-Sinclair, Jolieke van der Pols, H. Konrad Muller, Adele Green. Statistical analysis: Naomi Richmond-Sinclair. Obtained funding: Naomi Richmond-Sinclair and Adele Green. Administrative, technical, or material support: Naomi Richmond-Sinclair and H. Konrad Muller. Study supervision: Adele Green and Jolieke van der Pols.

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Role of the Sponsors: The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of data; or in the preparation, review, or approval of the manuscript.

Financial Disclosure: None reported.

Acknowledgment: We are indebted to Queensland Medical Laboratory and Sullivan Nicolaides Pathology for providing pathology reports for all study tumors.

All Financial Interests (including pharmaceutical and device products):

1. Employment Adèle Green and Jolieke van der Pols are employed by the Queensland Institute of Medical Research. Naomi Richmond-Sinclair is a student at the Queensland Institute of Medical Research. H. Konrad Muller is employed by Queensland Health Pathology Service.

2. Consultancies n/a
3. Honoraria n/a
4. Speakers bureau n/a
5. Stock ownership or options n/a
6. Expert testimony n/a
8. Patents n/a
9. Patent applications n/a
10. Royalties n/a
11. Donation of medical equipment n/a
Abstract

Objective
To investigate the relationship between incident basal cell carcinoma (BCC) and objective markers of cumulative sun damage to the skin.

Design, setting and participants
A randomly-selected sample of 97 incident BCCs that occurred during follow-up of participants in an Australian community-based study between 1992 and 2007 and for which diagnostic tissue was available for histologic assessment.

Main Outcomes Measures
Histologic dermal elastosis adjacent to the tumor and other markers of cumulative sun damage assessed by dermatologists prior to BCC occurrence, namely neck elastosis, telangiectasia, solar lentigines and solar keratoses, and the associations of these markers with BCC.

Results
Dermal elastosis was more likely to be seen adjacent to head and neck BCCs than trunk BCCs (p=0.01). Severity of dermal elastosis increased on each site with increasing clinical signs of cutaneous sun damage on that site. Among subsites of the head /neck itself, BCCs on neck (75%) and forehead (37%) most often showed adjacent severe elastosis while BCCs round the eyes showed the least (0%). All 55 people who developed head and neck BCCs had at least 3 different pre-existing signs of solar damage (including dermal elastosis) to skin of the face and neck, and
41 of the 42 people with trunk BCCs showed at least one pre-existing sign of solar damage to the skin of the trunk.

Conclusions

Histologic elastosis adjacent to BCCs generally reflects prevalent solar damage to skin in the same region. All BCCs on the head, and all but one on the trunk, developed in people who had objective signs of cumulative cutaneous sun damage in the corresponding anatomic region prior to BCC occurrence.
Introduction

Sun exposure is considered the major environmental factor associated with basal cell carcinoma (BCC) \(^1\), supported by evidence such as the strong inverse latitude gradient in incidence rates \(^2\) and an anatomic distribution that is consistent with general levels of sun exposure across body sites \(^3, 4\).

It has been debated however whether it is acute or cumulative sun damage that is necessary for BCC pathogenesis due to mixed results in relation to self-reported sun exposure \(^5-10\). For exploration of causal sun exposure, more reliable and objective measures than recalled sun exposure are needed and these include objective clinical signs or histologic evidence of photodamage. A small number of studies (three case-control \(^6, 7, 11\), one cohort \(^10\)) have shown, for example, that solar keratoses caused by long-term sun exposure, are significant risk factors for BCC. At the tissue level, two previous studies have measured the degree of histologic dermal elastosis in or adjacent to BCC tumors \(^12, 13, 14\). The first \(^12\), a Lebanese hospital-based study of 262 BCCs (95% from the head and neck), reported that 93% of BCCs were associated with some degree of solar elastosis. Facial subsites with the greatest proportion of BCCs that showed adjacent moderate/marked dermal elastosis were the nose, cheeks and forehead \(^12\). They also reported that 33% of BCCs had no or mild dermal elastosis, and paradoxically about half of these BCCs were from the head and neck. In a study of 175 BCCs (58% from the head and neck) diagnosed at assorted primary care and specialist clinics in the northern USA, 25% were observed to be associated with adjacent dermal elastosis \(^14\).
In the present study we have documented in a representative sample of BCCs from the head and neck and the trunk, the presence of adjacent dermal elastosis, along with other measures of long-term cutaneous sun damage to the skin of the head and trunk among affected participants. We also studied the relation of recalled number of sunburns as an objective sign of acute sun damage, to signs of chronic sun damage, in order to address the comparative roles of cumulative versus intense acute sun exposure in BCC development.
Materials and Methods

The Nambour Skin Cancer Study

Study participants were originally randomly selected in 1986 from the electoral register of all adult residents of the subtropical township of Nambour in Queensland, Australia (latitude 26°S), for a baseline study of skin cancer \(^1\). All participants completed a standard questionnaire at baseline about pigmentary traits including skin colour. During 1992 to 1996, participants took part in a field trial to assess sunscreen application and betacarotene supplementation in skin cancer prevention. Detailed descriptions of the community sample, field trial and its long-term outcomes have been published previously \(^15\)-\(^17\). In 1996, participants were invited to take part in a long-term follow-up study of skin cancer. Continuing participants provided written consent to have skin cancers notified to the investigators by regional pathology laboratories in Queensland, allowing 100% ascertainment of histologically confirmed BCCs, 1992 to end of follow-up in 2007. No participants were immunocompromised, and none had nevoid basal cell carcinoma syndrome. Ethical approval was obtained from the ethics committee of the Queensland Institute of Medical Research.

Cumulative photodamage and sunburn history

Participants were examined at baseline by dermatologists who documented standard signs of photodamage (photodamage of the neck, telangiectasia, solar lentigines, solar keratoses). In 1992, 1994 and 1996 information about sunburn history was
updated by questionnaire and dermatologists carried out full skin examinations. All clinical signs in a person predated diagnosis of their BCC. (For example, for a BCC diagnosed in 1995 the extent of photodamage was taken as the most severe recorded in either 1986, 1992 or 1994, but not 1996.)

*Basal cell carcinomas*

All BCCs were verified histologically. Investigators abstracted details of anatomic site from pathology reports and requested the tumor tissue for all BCCs from the relevant pathology laboratories. Among a total of 1202 BCCs, 489 had tumor tissue available upon request, 403 of which occurred on the head (typically sun-exposed) or trunk (not typically sun-exposed). From these 403, 97 tumors were randomly selected as a manageable number for histologic assessment.

*Elastotic stain and grading*

Degree of dermal elastosis was assessed in the normal skin immediately adjacent to the BCC tumor tissue using whole transverse cross-sections (5 mm) cut from formalin-fixed, paraffin-embedded tumor blocks. Sections were deparaffinized and rehydrated in 10mM citrate buffer (pH 6.0), stained with freshly prepared Verhoeff’s haematoxylin staining solution for 30 minutes, and following a water rinse, were dipped in 2% ferric chloride. The differentiation process was controlled by dipping the slide in containers of either ferric chloride or water, and continued until black elastic fibres were distinguishable. Slides were then rinsed in water for 2 minutes, treated with 95% alcohol for 2 minutes and again rinsed in water for 2 minutes.
Sections were counterstained with Van Gieson’s solution \(^{18}\) for 3 minutes, dehydrated directly into absolute alcohol, mounted and dried. For all BCCs a separate whole transverse cross-section stained with hematoxylin and eosin was available for histological reference.

Dermal elastosis was graded on an ascending scale from 0 to 3. Grade 0 referred to normal skin with no evidence of thickened elastic fibres. Increasing scores represented increasing numbers of fibres from a few scattered, to large aggregations of strongly stained elastic fibres, up to a distinct band of elastotic material (grade 3).

*Statistical analysis*

Fisher’s exact test was used to assess statistical differences and a p value less than 0.05 was considered statistically significant. All variables were treated as categorical variables. For the purposes of assigning a value to the degree of sun damage among those BCCs from people with similar evidence of sun damage, the modal category was chosen and where equal numbers of BCCs were associated with two categories the lower was chosen as the conservative estimate. Statistical analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina).
Results

Study population

The 97 BCCs included in this study had been diagnosed in 73 study participants, 35 males and 38 females, at an average age of 64 years. Among these 73 people, 13 had more than one BCC included in the study sample, of whom only one person had two BCCs diagnosed on the same date at the same anatomic site (the back). All BCCs were from either the head and neck (55 BCCs, 57%) or trunk (42 BCCs, 43%). Among the 73 people, 48 (66%) had fair skin and 25 (34%) had medium skin colour.

Perilesional dermal elastosis

Amongst the 97 BCCs, 70 (72%) had histological evidence of dermal elastosis of any grade (Figure 1). The majority of BCCs were associated with mild or moderate levels of dermal elastosis, 28% and 24% respectively. Twenty (21%) BCCs were associated with severe dermal elastosis.

The proportion of BCCs with associated dermal elastosis was similar among males and females (72% for males, 73% for females, p=0.16) and the degree of dermal elastosis increased with age at diagnosis (83% in those aged 60 years or older vs. 56% in those aged less than 60 years, p=0.02). There was no difference in the degree of dermal elastosis when BCCs from people with a single BCC were compared to those from people with multiple BCCs (67% vs. 74% respectively, p=0.655). This was also true when stratified by anatomic site and skin color.
Among the 55 BCCs from the head and neck, 42 (76%) had histological evidence of perilesional dermal elastosis. With regard to clinical markers of cumulative actinic damage on the skin of the head and neck, every BCC in the study sample was associated with one or more of the following: neck photodamage (Figure 2), telangiectasia, solar lentigines or solar keratoses. 25 (45%) BCCs came from 20 people all of whom had evidence of all five markers of cumulative cutaneous sun damage.

Among the 42 BCCs from the trunk, 26 (62%) had histological evidence of perilesional dermal elastosis. With regard to clinical markers of skin damage due to cumulative sun exposure to the trunk, all BCCs except for one were associated with solar lentigines and or solar keratoses. Of all BCCs on the trunk, 7 (17%) BCCs were from 6 people all of whom had evidence of all three markers of cumulative sun damage.

Among all BCCs, those from the head and neck were significantly more likely to be associated with dermal elastosis than BCCs from the trunk, 76% and 67% respectively (p=0.012, supplementary table). Specifically, 16 (29%) BCCs from the
head and neck were associated with a severe degree of dermal elastosis compared with 4 (10%) BCCs from the trunk.

With regard to anatomic subsites on the head and neck and trunk, Table 1 describes the presence and degree of dermal elastosis associated with BCCs. Whilst 58% of all head and neck BCCs had moderate to severe dermal elastosis, a higher proportion of the BCCs on the neck, and cheek and perioral subsites had moderate to severe dermal elastosis, 88% and 67% respectively. Conversely, 75% of the BCCs from the eye area had no dermal elastosis. Most BCCs from the back had nil/mild dermal elastosis (70%) and all chest BCCs had nil/mild dermal elastosis (Table 1).

*Recalled acute photodamage*

44 (80%) of head and neck BCCs and 39 (93%) of BCCs on the trunk occurred on 37 and 35 participants, respectively, who had reported a history of sunburns (Supplementary table). The single person who developed a trunk BCC without perilesional dermal elastosis or any other signs of cumulative sun damage reported experiencing at least 6 painful sunburns.
Discussion

In a random sample of 97 BCCs developed by participants in an Australian community-based cohort study, we found that every tumor except one occurred in conjunction with perilesional dermal elastosis and/or other cutaneous signs of cumulative sun damage in the associated anatomic region. Most BCCs occurred in people who had multiple signs of chronic photodamage. Furthermore our data showed that the great majority of people affected by the 97 study BCCs reported suffering acute photodamage as well (usually multiple times).

Numerous studies have assessed the effects of sun exposure on BCC risk. Previous studies, however, have been limited to a single BCC from affected people only \(^{19, 20}\) and have sometimes excluded people with a previous skin cancer \(^{20}\). The findings from studies like these and larger descriptive studies of BCC’s anatomic distribution \(^{22, 23}\) have led to the hypothesis that BCCs occurring on the head and neck have a different sun-related etiology to BCCs on the trunk. In contrast, this study has studied representative samples of all BCCs from a community-based cohort with diagnostic tissue available and shown that almost all have developed in those who have pre-existing signs of long-term photodamage, on the anatomic site of BCC occurrence. Further, virtually every BCC (with the exception of one on the trunk) was unique according to date and/or site including from the same person, and therefore could contribute independently to the study.

Given the strong evidence for sun exposure in BCC pathogenesis we expected that all of the BCCs in this series would have some degree of perilesional dermal...
elastosis but our findings showed some 28% of BCCs had no histological evidence of perilesional elastosis, including 24% of head and neck BCCs. The proportion of BCCs in this study without perilesional dermal elastosis is somewhat higher than the 7% reported by Zaynoun et al. 12 to be without dermal elastosis. Another study from the temperate northern USA with roughly equal numbers of BCCs from the head and neck, and from the trunk, reported a lower prevalence of perilesional dermal elastosis at 25% which is most likely due to the lower ambient UV environment from which these BCCs arose 14.

One previous study has also investigated the anatomic subsites of BCC in relation to the degree of perilesional dermal elastosis 12. Similar to our findings they reported that the anatomic subsites with the greatest proportion of BCCs with no or mild dermal elastosis were the eyes and the ears. There were some differences in our findings however. Unlike our findings, the study by Zaynoun and colleagues 12 showed that some BCCs from the eye area did have perilesional dermal elastosis where we had no BCCs from the eyes with this histological skin change. This suggests that dermal elastosis can develop across all facial subsites. Although a third of the BCCs had no evidence of associated dermal elastosis virtually all were associated with cumulative photodamage. This suggests that cumulative sun exposure is necessary for the pathogenesis of the majority of BCCs. Usually (in 86% of cases) the pre-existing chronic signs were accompanied by a history of acute photodamage (sunburns), in agreement with a body of evidence to date also showing that self-reported histories of sunburns are strongly associated with general BCC risk 5-7. 10. There is a literature surrounding the questionable reliability of
sunburn recall among adults \textsuperscript{24, 25} making it a less robust measure of photodamage than the other more objective measurements used in this study.

With regard to study limitations, only a restricted number of BCCs could be included in this study, even though they were chosen at random. This placed a constraint on the statistical power of the study. With regard to sunburns, beyond the poor reliability of past sunburns, nor could we be sure exactly which anatomic site/s were affected by the sunburn, and thus we were unable to assess the effects of acute sun damage on specific body sites in relation to site of BCC development.

We conclude that BCC carcinogenesis is inextricably associated with cumulative photodamage to the particular site of BCC occurrence. It appears that the most important aspect of previous sun exposure is the total UV dosage received by the epidermis (at the target cell level) rather than the pattern (cumulative or acute) whereby it was received.
References


Figures

Figure 1  Photomicrographs of perilesional elastotic changes adjacent to basal cell carcinomas nil (A), mild (B), moderate (C) and severe (D).
Figure 2  Examples of skin of the neck with (A) no-mild photodamage, (B) moderate photodamage or (C) severe photodamage.
Tables

Table 1  Degree of solar elastosis associated with basal cell carcinomas according to anatomic subsite in Queensland, Australia

<table>
<thead>
<tr>
<th>Anatomic subsite</th>
<th>Degree of solar elastosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nil</td>
</tr>
<tr>
<td><strong>Head &amp; Neck</strong></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>13 (24%)</td>
</tr>
<tr>
<td>Forehead &amp; temple</td>
<td>3 (27%)</td>
</tr>
<tr>
<td>Ears</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>Eyes</td>
<td>3 (75%)</td>
</tr>
<tr>
<td>Nose</td>
<td>5 (36%)</td>
</tr>
<tr>
<td>Cheek &amp; perioral</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Neck</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Trunk</strong></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>14 (33%)</td>
</tr>
<tr>
<td>Back</td>
<td>11 (30%)</td>
</tr>
<tr>
<td>Chest</td>
<td>3 (60%)</td>
</tr>
</tbody>
</table>
### Supplementary data

**Supplementary Table 1** Markers of acute and long term skin damage associated with basal cell carcinomas (BCC) in Queensland, Australia

<table>
<thead>
<tr>
<th>Number of BCCs</th>
<th>Head and neck</th>
<th>Trunk</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Elastosis</td>
<td>photodamage</td>
<td>Telangiectasia</td>
<td>Solar keratoses</td>
<td>Solar lentigines</td>
</tr>
<tr>
<td>25 (45%)</td>
<td>Severe</td>
<td>Severe</td>
<td>Severe</td>
<td>≥5</td>
<td>1 to 10</td>
</tr>
<tr>
<td>7 (13%)</td>
<td>Nil</td>
<td>Moderate</td>
<td>Severe</td>
<td>≥5</td>
<td>1 to 10</td>
</tr>
<tr>
<td>7 (13%)</td>
<td>Moderate</td>
<td>Severe</td>
<td>Moderate</td>
<td>≥5</td>
<td>1 to 10</td>
</tr>
<tr>
<td>5 (9%)</td>
<td>Moderate</td>
<td>Severe</td>
<td>Moderate</td>
<td>≥5</td>
<td>Nil</td>
</tr>
<tr>
<td>2 (3.6%)</td>
<td>Severe</td>
<td>Moderate</td>
<td>Nil</td>
<td>1 to 4</td>
<td>1 to 10</td>
</tr>
<tr>
<td>1 (1.8%)</td>
<td>Moderate</td>
<td>Nil-mild</td>
<td>Moderate</td>
<td>Nil</td>
<td>1 to 10</td>
</tr>
<tr>
<td>2 (3.6%)</td>
<td>Nil</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>2 (3.6%)</td>
<td>Nil</td>
<td>Moderate</td>
<td>Moderate</td>
<td>1 to 4</td>
<td>1 to 10</td>
</tr>
<tr>
<td>1 (1.8%)</td>
<td>Severe</td>
<td>Moderate</td>
<td>Moderate</td>
<td>≥5</td>
<td>Nil</td>
</tr>
<tr>
<td>1 (1.8%)</td>
<td>Mild</td>
<td>Moderate</td>
<td>Nil</td>
<td>Nil</td>
<td>1 to 10</td>
</tr>
<tr>
<td>1 (1.8%)</td>
<td>Nil</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Nil</td>
<td>1 to 10</td>
</tr>
<tr>
<td>1 (1.8%)</td>
<td>Nil</td>
<td>Moderate</td>
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CHAPTER 7

DISCUSSION
Broadly, this collection of specific, connected studies sought to better understand the epidemiology of BCC. In particular it aimed to address key knowledge gaps in the field: to document the incidence of BCCs with a focus on the occurrence of multiple BCCs and their body distribution, and also to document how constitutional and environmental factors contribute to the occurrence of multiple BCCs within individuals, the anatomic distribution and histologic subtypes of BCC. Furthermore, this research project addressed these gaps in knowledge through a unique epidemiological platform: a community-based prospective study.

As illustrated in Figure 7.1, new outcomes can be added on two levels to refine the epidemiological understanding of BCC in the context of recently published studies. Study limitations have been discussed below, alongside the strengths. This is followed by an exploration of recommended future work in this area.

Inclusive approach to research methodology for BCC

In consideration of the vast BCC literature, few studies have actually researched the phenomenon of multiple BCCs per person (key articles include: (Marghoob et al., 1993; Raasch and Buettner, 2002; Ramachandran et al., 2009; van Iersel et al., 2005) (All references in Chapter 7 can be found in the final List of References). This is a consequence of the fact that most previous BCC investigations stem from studies of the case-control or cross-sectional design (key articles include: (Gallagher et al., 1995; Naldi et al., 2000; Pelucchi et al., 2007; Rosso et al., 1996), so the data required to support explicit research into BCC multiplicity were often not available. Further, previous BCC studies that were founded on the prospective study design often restricted their investigations to the first BCC for each person (Neale et al., 2007) or did not acknowledge multiple BCCs (Han et al., 2006; van Dam et al., 1999). Whilst these previous studies were insightful and contributed to an increase in BCC information, it is possible they did not sufficiently assess BCC because for those people who had had more than one BCC they
analysed only part of their disease occurrence. Multiplicity of BCC should be an important consideration for future research projects: findings of BCC investigations that account for the full disease complement for each person will more accurately reflect BCC biology.

Another important consideration is that the association between BCC and its major environmental risk factor, sun exposure, becomes stronger with time. This is reflected most clearly in the increase of BCC incidence with older age, suggesting the association is time- and/or dose-dependent. In the case of
multiple BCCs, people may develop them over time, at different ages. It is therefore necessary to account for the timing of the exposure in relation to each BCC’s development. This approach was taken in this research project, such that if a person, for example, experienced a BCC in 1993 the exposure data predated 1993. In the Nambour Study exposure data were collected in 1986 and 1992 so data from these years could be analysed in relation to the BCC diagnosed in 1993. If the person were then to develop another BCC, four years later, in 1997, the exposure data used still predated the date of diagnosis for this lesion. After 1992, exposure data were updated in 1994 and 1996, hence data from these years could also be analysed in relation to the BCC diagnosed in 1997 or any BCC that occurred newly after these data collections. This approach was critical for analysing data about cutaneous markers of photodamage, including solar keratoses and elastosis that change with time.

As above, it is by virtue of the prospective and community-based design of the Nambour Skin Cancer Study that this research project was afforded the opportunity to consider the multiplicity of BCC in all investigations. In each aspect of this research project all people affected by BCC and all known BCCs developed by those people have been included. In some cases this required an analytical approach that accounted for the intra-person correlation when more than one BCC came from the same person (repeated measures analysis). This approach is rarely used in the research of BCC (Karagas et al., 1992; Pandeya et al., 2005). By having taken this all-inclusive approach this research project can substantially advance the understanding of BCC.

Identification of the magnitude of the burden of multiple BCCs and associations with multiple BCCs (Papers 1 and 3)

It is widely acknowledged that BCC is the most common malignancy among fair-skinned populations. However, true incidence estimates are sparse because BCCs are not routinely registered. Incidence estimates have largely come from ad hoc studies. In North America and Europe (Bath-Hextall et al.,
incidence estimates are typically an order of magnitude lower than corresponding estimates for Australia. A survey in 2002 of over 57,000 Australians estimated an age-standardised incidence rate of 884 BCCs per 100,000 persons (Staples et al., 2006). No previous estimates however have accounted for the occurrence of multiple BCCs per person and it is likely therefore that these previous studies underestimated the true BCC incidence. Using up-to-date data from the Nambour Skin Cancer Study this research project has generated the most recent incidence estimates for BCC in the Australian population: the overall age-standardised incidence of BCC was 1541 people per 100,000 pyar, 1813 per 100,000 pyar among men and 1269 per 100,000 pyar among women. These are the highest cancer incidence estimates ever published.

Incidence overall was broken down into incidence of persons affected by a single BCC: 935 per 100,000 pyar and by multiple BCCs: 705 per 100,000 pyar. Similar to previous reports (Bath-Hextall et al., 2007a; Karagas et al., 1999; Staples et al., 2006), for both males and females, all incidence estimates increased steadily with age and incidence was low before the age of 40 years. More males than females were affected by BCC. The overall findings reinforce the high rate at which BCCs occur and reveal for the first time the rate of occurrence of multiple BCCs among people who reside in a high UVR environment.

Most previous studies of BCC that have made mention of multiple BCCs have limited this to a brief adjunct statement about the proportion of people affected by multiple BCCs. In New Hampshire, USA, multiple BCCs occurred in 16% of affected patients in a 2-year period (Karagas et al., 1999), while in a tropical Australian community, 26% of BCC patients were treated for multiple BCCs in a 3-year period (Raasch and Buettner, 2002). A follow-up hospital-based study in the Netherlands reported the five-year risk for a subsequent BCC was 30% (van Iersel et al., 2005) and in a meta-analysis of seven American-based studies with up to seven years follow-up, this figure was 53% (Marghoob et al., 1993). It was generally unclear previously whether the multiple BCCs were diagnosed at the same time or different
times. In comparison this research project showed that over a 10 year period in a high incidence population, 46% of those sporadically affected by BCC experienced multiple BCCs and when observation was extended by 6 years, to a period of 16 years, this figure climbed to nearly 60%. Among our study participants affected by multiple BCCs, 29% were diagnosed with two or more BCCs on the same date. These estimates of the proportion of people affected by more than one BCC are broadly consistent with the previous estimates from other studies of sporadic BCCs given the longer period of follow-up in this research study. They also indicate that those affected by multiple BCCs tend to be affected over time.

We also documented in detail the anatomic distribution of BCCs among persons affected sporadically by more than one BCC. A previous study with a mean follow-up time of two and a half years and limited only to those patients with a first BCC on the head and neck or the trunk, described in broad terms how people with multiple BCCs tended to develop them on a single site, in particular patients with a first BCC on the trunk (Ramachandran et al., 2001). The investigators did not, however, present any indication of the proportion of people who developed BCC on a single or more than one anatomic site. Further, the follow-up time in their study was limited to a small snap-shot of the true amount of time a person remains at risk of developing subsequent BCCs. On the other hand a hospital-based study in the Netherlands with a median follow-up time of 3.1-years showed that 33% of people affected by multiple BCCs were affected across different sites (van Iersel et al., 2005), and in an American study, 45% of people affected by multiple BCCs developed BCCs on different anatomic sites during 7-years of follow-up (Marghoob et al., 1993). In the present research study, with 16-years of follow-up, 60% of those with multiple occurrences of BCC developed them on more than one anatomic region. Further, among those who developed two to three BCCs, the most common site combination was to have both the head and neck, and trunk affected. And among those with four or more BCCs, the tumors usually occurred on the head and neck, limbs and trunk. Overall the pattern of tumor occurrence across anatomic sites was similar, whether people had a single BCC or multiple BCCs, with the head
and neck by far the most commonly affected site. The site-specific incidence estimates were consistent with the level of sun exposure reaching each site, in agreement with other studies (Bastiaens et al., 1998; Buettner and Raasch, 1998; Franceschi et al., 1996). In general, people affected by multiple BCCs tend to develop them across more than one anatomic site.

These multiple incidence figures in conjunction with the latest overall incidence estimates are striking and make it apparent that the actual BCC tumour burden is greater in a population than is evident simply from incidence rates of general BCC occurrence per person. They give some indication as to why treatment of BCC consumes a substantial proportion of annual health spending in Australia (AIHW, 2005), North America (Chen et al., 2001) and Europe (Morris et al., 2005). The commonness of multiple BCCs, and the fact that those who have multiple BCCs tend to be affected across more than one anatomic site, have a two-fold public health relevance. Firstly for people affected by BCC there is a clear need for regular skin checks and these follow-up checks should be inclusive of the whole body, even sites that are not typically sun exposed. This will increase the opportunity for early detection and treatment of subsequent BCC among people previously affected. Secondly, the knowledge about anatomic sites of BCC predilection can be translated directly into specific evidence-based health messages about sun-protection. The prevention of basal cell carcinoma can be achieved by the avoidance of excessive UV exposure especially to the head and neck, and in particular, the nose. In terms of scientific value, the frequency of people with multiple BCCs being affected on more than one anatomic site suggests a common pathogenic mechanism is shared by BCCs across sites (see below). This research project provides insight into the potential magnitude of the BCC tumour burden in Caucasian populations, especially those living in places of intense sun exposure or frequently holidaying in such places.
BCCs have strong associations with clinical signs of early life sun exposure and cumulative photodamage

Sun exposure is considered the major environmental factor for general BCC pathogenesis (Rubin et al., 2005). Previous studies have shown that the nodular growth pattern is the most common (Boi et al., 2003) and nodular BCCs tend to occur on the head and neck (Bastiaens et al., 1998; Boi et al., 2003). This is the site most commonly treated for BCC (Raasch et al., 2006) and has a greater opportunity for sun exposure than the trunk where superficial BCCs, the second most common subtype mostly occur (Bastiaens et al., 1998; Raasch et al., 2006). These previous observations led to the hypothesis that BCCs of different histological subtypes or different sites of occurrence have different sun-related etiologies (Pelucchi et al., 2007; Scrivener et al., 2002). The majority of studies that have supported this hypothesis however have been based on assorted large series of retrospectively collected pathology reports. In the current study we were in a strong position to be able to assess BCCs on different anatomic sites for their relationship to sun exposure, because markers of chronic sun damage at each site of occurrence could be used to test for site-specific associations. Among people with facial telangiectasia, solar lentigines and solar keratoses the odds for developing a BCC on the head and neck was 2-fold higher than people without these signs of photodamage. Similarly for people with solar lentigines or solar keratoses on the trunk the odds for developing a BCC at this site were about 3-fold higher than the odds for people without these skin changes. This site-specific association was also seen for BCC on the limbs: among people with solar keratoses on the limbs the odds for developing a BCC were nearly 4 times higher than for people without solar keratoses on the limbs. These findings suggest that BCCs regardless of anatomic site of occurrence are strongly associated with previous high solar ultraviolet radiation exposure.

With regard to the above-mentioned hypothesis that BCCs of different histological subtypes have different sun-related aetiologies, it was not clear, based on the evidence available, if the risk was mainly determined by the
anatomic site, the sun exposure histories of the host, or some other factors. This is because the only study to have assessed risk factors for nodular and superficial BCCs separately did not account for anatomic site of occurrence (Pelucchi et al., 2007). In this thesis the importance of clinical markers of sun damage was also assessed in relation to BCC’s two major histological growth patterns, nodular and superficial. Present analyses were stratified by anatomic site to ensure that the associations were not due to the different opportunity for sun exposure on the head and neck, and the trunk. For BCCs on the head and neck and those on the trunk a history of five or more painful sunburns was strongly associated with nodular and superficial BCCs. Strong associations with increasing solar keratoses counts were evident for both BCC subtypes on each site when compared to people with no solar keratoses. These results suggest that BCCs of different histological growth patterns appear to have similar aetiologies which suggests that the growth patterns of BCCs are determined by their micro-environment (the skin at the anatomic site) perhaps influencing the target cell rather than the external environment (sun exposure history).

With regard to multiple BCCs within a person, a limited number of previous studies in selected clinical populations have suggested that multiple BCC occurrence is associated with increasing age (van Iersel et al., 2005) and fair skin (Lovatt et al., 2005; Ramachandran et al., 1999), but little was known about the importance of sun exposure history and photodamage over time, in the development of sporadic multiple BCCs. Skin complexion was not associated with multiple BCCs among all people affected by BCC. We next assessed if sun exposure history was able to distinguish between people with single versus multiple BCCs but after prolonged follow-up found no association between reported recreational or occupational sun exposure and the occurrence of intermediate or high numbers of BCCs versus single BCC. Nor did we find any evidence that the number of sunburns, a measure of acute sun damage, was associated with multiple BCCs. We did however; find that melanocytic nevi on the forearm but not the back are associated with multiple BCCs later in life. Given the difference in melanocyte biology across sites (those on the trunk require less cumulative sun exposure than
melanocytes on other site to undergo changes) suggests that there is more than simple nevus propensity playing a role and that it likely reflects the importance of childhood sun exposure influencing risk. The most striking observed difference between the patient groups was that the odds for developing many BCCs were over 4-fold higher among participants who had high numbers of solar keratoses. Other measures of photodamage, facial telangiectasia and solar elastosis, were not associated with multiplicity of BCC among cases.

Given the apparent importance of photodamage to BCCs, it was hypothesised as part of this research project that all BCCs would have evidence of perilesional solar elastosis, a histological marker of cumulative photodamage. This was not observed to be true however. Among the unselected 55 head and neck BCCs sampled, 25 BCCs (45%) were from 20 people who had facial elastosis, telangiectasia, solar keratoses, solar lentigines and perilesional solar elastosis. Among the 42 truncal BCCs sampled, 28 BCCs (67%) were from 25 people who had a history of at least two clinical signs of photodamage (truncal solar keratoses, solar lentigines, perilesional solar elastosis) and 17% had evidence of all three of these skin changes. Overall, most BCCs occurred in people who had multiple signs of chronic photodamage and every tumour except one occurred in conjunction with perilesional elastosis and/or other cutaneous signs of cumulative sun damage in the associated anatomic region. BCCs from the head and neck were significantly more likely to be associated with perilesional elastosis than BCCs from the trunk and severity of dermal elastosis increased on each site with increasing clinical signs of cutaneous sun damage on that site. BCC carcinogenesis appeared to be inextricably associated with cumulative photodamage to the particular site of BCC occurrence.

The results generated from this research project challenge the view that BCCs on different body sites or of the nodular or superficial growth patterns are different in their association past sun exposure. The analyses presented in this thesis differ somewhat to those of previous studies because participants’ subsequent BCCs were taken into account for analyses where
the site of occurrence was the outcome and when histological subtype was the outcome, the site of occurrence was accounted for. This approach meant there was less opportunity for confounding in our analyses. Our findings suggest that all BCCs have similar aetiologies in the sense that they are strongly associated with experience of high sun exposure. This was observed consistently when considering BCC site of occurrence, nodular and superficial growth patterns, and multiple BCC occurrences. Further the site-specific prevalence of photodamage, especially solar keratoses, can be regarded as evidence for, and personal dosimeters of, chronic sun damage to the site affected. Thus our data indicate that persons who develop multiple BCCs have received a greater dose of solar UVR than people with a single BCC in general. A history of sunburns, however, was associated with BCC histology but not site or multiplicity. This is likely to be because these analyses included only people affected by BCC, whereas the former included a reference group of people who were unaffected by BCC. For this reason it is possible that sunburn is associated with BCC multiplicity and site when comparisons are made to people unaffected by BCC. Given the observation that not all BCCs have histologic evidence of perilesional photodamage but are associated with photodamage at the general site of occurrence, even for BCCs across different sites, suggests a common pathogenic mechanism is shared by BCCs. This study’s finding that the association between forearm nevi and increased odds for BCC on the head and neck and trunk is stronger when the individual has reported a high lifetime sun exposure history further supports this theory. In terms of scientific value it is apparent from our findings that BCCs can and do arise in specific anatomic sites that do not have histological evidence of severe sun damage, suggesting that BCC carcinogenesis occurs prior to severe and long term photodamage. The public health relevance of this is that BCCs, regardless of site, histology, order of occurrence can be prevented through limiting the cumulative amount of sun exposure. These findings suggest that control of BCC multiplicity in the population at large is feasible through decreasing cumulative sun exposure, thereby helping to curb the substantial encumbrance that BCC places on health systems serving white populations.
Limitations

As above, the strengths of this study were the longitudinal data collection and the community-based sample who were representative of their community at large (Green et al., 1994), with complete ascertainment of all histologically-confirmed BCCs in a 16-year period. Despite its strengths, this research project is not without limitations. Whilst some participants had a BCC prior to the observation period, the BCC records for that time were incomplete for some participants. Therefore certainty about the BCC status of all participants was only possible for the 16-year observation period. Due to the substantial length of follow-up time the data upon which this thesis is based represent the typical BCC-experience of a community during a window of 16 years. The analyses were, however, repeated in the sub-group of participants who reported that they did not have previous BCC (n=335) and similar results were obtained, thus we believe this has not influenced our findings to any material extent.

A second epidemiological limitation inherent in the data collected as part of the Nambour Skin Cancer Study is that a retrospective evaluation of some exposure information was required. In particular information about sun exposure, including: sunburns, recreational and occupational histories. Due to the longitudinal nature some of the information was collected on repeated occasions. It is possible therefore that some participants provided some information following the diagnosis of a skin cancer and thus the diagnosis may have affected their accuracy of recall. The lack of association between recreational and occupational sun exposure history and BCC (multiplicity, site of occurrence and histology) may be explained by the phenomenon where people especially at low latitudes, self-select occupations to which they are suited (more olive skinned people working in outdoor occupations (Green et al., 1996)). Regarding sunburn history, there is mixed literature surrounding the reliability of sunburn recall among adults (Berwick and Chen, 1995; Shoveller and Lovato, 2001; van der Mei et al., 2006). This may be attributed to the acute nature of sunburns, making it a subjective measure of sun damage than other more objective measurements. Also the disparate
prevalence of sunburn between countries and studies (going from extremely common in Australian to rare in some European populations) may give invalid recall. Consequently this study’s estimates of the acute intense pattern of sun exposure in a high prevalence setting may not reflect the true association. Further it is uncertain exactly which anatomic site/s were affected by sunburn, which limited the assessment of the site-specific effects of acute sun damage. This uncertainty, however, was offset somewhat by the use of objectively measured clinical markers of cumulative sun damage. Markers of chronic photodamage such as solar keratoses flag a history of long-term sun exposure (Rossi et al., 2007) and thereby remove the error when recall is used to assess the amount of past sun exposure a person has experienced. Interpretation of findings in relation to photodamage and BCC in general are strongly indicative of the role of overexposure to UVR but not the specific aspects of that overexposure, for example the pattern and exact dose received. Interpretations of the perilesional elastosis data were limited due to the restricted number of BCCs assessed; there was not sufficient statistical power to test for differences between various subgroups. Thus this research study has not been able to specifically identify which aspects of long-term/intense UV exposure cause BCC pathogenesis.

This thesis presented odds ratios as an estimate of the level of risk associated with the exposures. Although all data for this research study were taken from a cohort study and relative risk estimates would normally be expected from such data, due to the nature of BCC occurring multiple times in some people and the polytomous outcome variables used in these analyses, a multinomial log regression, where repeated measures can be accounted for, would have been the most appropriate approach. This was not possible for this student to perform at the time of analysing these data and thus multinomial logistic regression with repeated measures was used. Relative risk estimates were generated, however, using binomial logistic regression, and the magnitude of the estimates was similar (data not shown).
Future directions

Although this research project has made a substantial advancement in our understanding of BCC, a significant amount of further work is still needed to fully explore the implications of the findings. Future work is required on two levels: the medical research and public health platforms.

Medical research

A critical step in furthering our understanding of BCC and ultimately reducing the burden of this skin cancer lies in understanding the role that molecular factors play in BCC pathogenesis. A key goal of future studies should be to relate the patient phenotype and clinical cancer profile to a list of defining genomic, proteomic and immunologic principles. For this to happen it will be critical to pursue an integrated approach, through the combination of epidemiologic and laboratory-based disciplines.

Whilst much information is known about genetic aberrations associated with sporadic BCC development, (including in Patched-1, smoothened, and p53), the role of detoxifying proteins (like GST) and immunological factors, future studies need to understand what this information means in light of other relevant data in order to turn this information into useful knowledge about the cancer. Future studies should focus on whether these factors vary according to fundamental aspects of the skin cancer and its host, including site of occurrence, histology, the multiplicity of BCC, past history of skin cancer and host phenotype information. Further, the pooling of resources between studies (for example, using tissue samples from the Nambour Skin Cancer Study and other prospective population-based datasets) to boost sample size and the generalisability of results will make the most of the opportunities that interdisciplinary research can provide. The ultimate goal of these studies should be to understand how elements at the sub-human level influence responses to exposures at the environmental level and vice versa.
In contrast to many other cancers, skin cancers, including BCC are largely preventable. Prevention efforts for BCC often occur in conjunction with other skin cancers because they each share the same major environmental exposure – ultraviolet radiation. In order to advance prevention efforts, changes to primary and secondary prevention approaches are necessary.

Primary prevention efforts should be centred on the effective communication of skin cancer information and evidence-based prevention messages. This information should be disseminated widely, including to people of all ages and residing in all locations within Australia. It should be made readily available through a variety of sources including, the internet, newspapers, pamphlets, TV and radio. Further, specific prevention messages should be created for key populations that have been identified as being at risk of high levels of sun exposure or being especially susceptible to skin cancer (for example, solid organ transplant patients). Just as these prevention strategies should encourage the individual to be sun-aware, they must also target the relevant bodies responsible for providing infrastructure to the community, such that they provide improved shade design, including tree planting for outdoor areas. All in all primary prevention efforts should continue to focus on the reduction of intense acute and cumulative sun exposure throughout a person’s life, such as through midday sun avoidance and the targeted use of protective clothing and sunscreen on those sites that sustain the greatest amount of sun exposure.

With regard to primary prevention I suggest two actions for the continued and better prevention of skin cancer:

1. The Australian government (www.skincancer.gov.au) endorses an awareness campaign that encourages people not rely on a single means of sun protection. This could be encouraged at the many Australian schools. For example, the current “No hat. No play” policy
could be extended by to include sunscreen: “No hat or sunscreen. No Play”.

2. Theoretically, if a person adheres to skin cancer prevention guidelines their risk for skin cancer should be minimised. Realistically though there are a number of barriers that discourage some people from taking these actions and one of them is the purchase of sun-protective clothing and sunscreens. I suggest therefore that the government provide subsidy for the cost of these items thus making them more readily available to the community at large.

In terms of secondary prevention, it will be important for all individuals affected by BCC, especially those with photodamage, to be monitored by health care professionals for the development of subsequent BCCs. Furthermore patient education should focus on the key warning signs of BCC: clinical markers of photodamage.

Finally, efforts should also be directed toward monitoring and evaluating the existing prevention programs and revitalising them, in light of new evidence-based research information, when needed.

_These actions will ultimately lead to a better understanding of what causes BCC and how best to control the onset of this disease._
List of References


Jacob A (1827) Observations respecting an ulcer of peculiar character, which attacks the eye lids and other parts of the face. The Dublin Hospital Reports 4:232-39.


APPENDICES
Appendix 1

Publication of work partly performed during the PhD but unrelated to the main thesis topics:

*Histologic and epidemiologic correlates of P-MAPK, Bm-2, pRb, p53, and p16 immunostaining in cutaneous melanomas*
Due to copyright restrictions, this article is not available here. Please consult the hardcopy thesis available from QUT Library or view the published version online at:

http://dx.doi.org/10.1097/CMR.0b013e32830d8329
Appendix 2

Key publications from the Nambour Skin Cancer study

*The Nambour Skin Cancer and Actinic Eye Disease Prevention Trial: Design and Baseline characteristics of Participants*

*Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial*
Due to copyright restrictions this appendix is not available online. Please consult the hardcopy thesis available from the QUT Library.
Appendix 3

Studies presenting the association between selected pigmentary characteristics, sunburn and sun exposure measures and basal cell carcinoma
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<td>Naldi et al, 2000, Italy, Italian Group for Epidemiological research in Dermatology</td>
<td>Case-control: 528 cases with incident histologically confirmed BCC diagnosed in hospital study centres, 512 non-dermatology patients of same hospitals, 1995-1996</td>
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<td>Skin reaction to sun exposure</td>
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<td>Skin reaction to sun exposure: usually burns with no or little tan</td>
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<td>11+</td>
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<table>
<thead>
<tr>
<th>Reference, location, study name</th>
<th>Study description</th>
<th>Exposure assessment</th>
<th>Exposure categories</th>
<th>Risk estimates</th>
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<tbody>
<tr>
<td>Vlajinac et al, 2000, Belgrade and Zrenjanin, Yugoslavia, 1996-1997</td>
<td>Case-control: 200 consecutive cases at skin departments, 100% histologically confirmed, 399 non-cancer dermatology patients from same skin departments</td>
<td>Interviewer-administered standard questionnaire</td>
<td>Eye colour: brown</td>
<td>0.09 (0.02-0.37)</td>
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<td>Skin reaction to sun exposure: usually burns with no or little tan</td>
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<thead>
<tr>
<th>Reference, location, study name</th>
<th>Study description</th>
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<th>Exposure categories</th>
<th>Risk estimates</th>
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<tbody>
<tr>
<td>Kricker et al, 1991, Geraldton, Australia,</td>
<td>Case-control: 201 cases with incident BCC from population survey, 100% histologically confirmed, 700 controls who were disease free at population survey/year prior</td>
<td>Personal calendar and interviewer-administered standard questionnaire</td>
<td>Hair colour</td>
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<th>Reference, location, study name</th>
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<tbody>
<tr>
<td>Zanetti et al, 2006, 14</td>
<td>Case-control: 215 male cases with</td>
<td>Interviewer administered</td>
<td>Hair colour</td>
<td>1.0</td>
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<tr>
<td>centres in Italy, Spain, France, Portugal, Denmark, Germany, Argentina, 2001-2002</td>
<td>incident BCC diagnosed in hospitals, 100% histologically confirmed. 349 non-dermatology male patients of same hospitals as controls</td>
<td>standard questionnaire</td>
<td>Brown</td>
<td>1.6 (1.07-2.52)</td>
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<td>Blonde</td>
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<td>Light blonde/red</td>
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<td>Eye colour</td>
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<td>Tendency to tan</td>
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<td>Some</td>
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<td>Sunburns during lifetime</td>
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<td>Often</td>
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<table>
<thead>
<tr>
<th>Kricker et al, 1991, Geraldton, Australia, 1987</th>
<th>Case-control: 226 cases with histologically confirmed BCC, 1015 controls with no skin cancers</th>
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<td>Propensity to burn</td>
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<td>Burn/then tan</td>
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<td>Burn/blisters</td>
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<td>40+</td>
<td>10.44 (5.81-18.78)</td>
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<th>Han et al, 2006, USA, Nurse's Health Study</th>
<th>Nested case-control study, 283 cases, 804 controls</th>
<th>Retrospective self-administered questionnaire</th>
<th>Severe sunburns in lifetime</th>
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<td>1.37 (0.81-2.21)</td>
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<tr>
<th>Green et al, 1996, Nambour, Australia, Nambour Skin Cancer Study</th>
<th>1675 randomly selected adults from community register, skin cancer diagnoses followed up 1985-1992, 250 BCC cases</th>
<th>Self-administered questionnaire,</th>
<th>Skin colour</th>
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<td>Blonde/light brown</td>
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<td>Red/auburn</td>
<td>1.81 (1.12-2.82)</td>
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<td>Number of melanocytic nevi on arms and hands</td>
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<td>1 to 10</td>
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<thead>
<tr>
<th>Van Dam et al, 1999, USA, Health Professionals ’ Follow-up Study</th>
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<tbody>
<tr>
<td>44 951 male health professionals, including 3273 BCC cases, 1986-1994</td>
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<thead>
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<th>Self-administered questionnaire Hair colour</th>
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<tr>
<td>Black</td>
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<tr>
<td>Dark brown</td>
<td>1.08 (0.93-1.25)</td>
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<tr>
<td>Light brown</td>
<td>1.15 (0.99-1.34)</td>
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<tr>
<td>Blonde</td>
<td>1.13 (0.94-1.35)</td>
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<tr>
<td>Red</td>
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<thead>
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<th>Eye colour</th>
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<tbody>
<tr>
<td>Brown</td>
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<tr>
<td>Hazel/green</td>
<td>1.19 (1.07-1.32)</td>
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<td>Blue</td>
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<table>
<thead>
<tr>
<th>Skin reaction to sun exposure as an adolescent</th>
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<tbody>
<tr>
<td>Tan, not burn</td>
<td>1.51 (1.37-1.67)</td>
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<tr>
<td>Burn, then tan</td>
<td>2.13 (1.90-2.38)</td>
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<tr>
<td>Painfully burn, then peel</td>
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<table>
<thead>
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<th>Melanocytic nevi on arms</th>
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<tbody>
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<td>None</td>
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<td>1 to 2</td>
<td>1.27 (1.14-1.41)</td>
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<td>3 to 5</td>
<td>1.29 (1.11-1.50)</td>
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<tr>
<th>Sunburns during lifetime</th>
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<tr>
<td>1 to 2</td>
<td>1.14 (1.00-1.30)</td>
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<td>1.20 (1.05-1.38)</td>
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<td>6 to 9</td>
<td>1.33 (1.14-1.54)</td>
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<tr>
<td>10+</td>
<td>1.49 (1.30-1.71)</td>
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<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Case-control: 226 male cases with incident BCC identified from cancer registry, 100% histologically confirmed, 406 male controls selected from population based health register</td>
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<table>
<thead>
<tr>
<th>Interviewer administered standard questionnaire Skin colour</th>
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<td>Dark</td>
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<td>Medium</td>
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<th>Hair colour</th>
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<tr>
<td>Brown</td>
<td>0.6 (0.3-1.4)</td>
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<tr>
<td>Blonde</td>
<td>0.6 (0.3-1.4)</td>
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<tr>
<td>Red</td>
<td>2.1 (0.7-2.2)</td>
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<thead>
<tr>
<th>Eye colour</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>1.0</td>
</tr>
<tr>
<td>Hazel</td>
<td>1.7 (0.9-3.1)</td>
</tr>
<tr>
<td>Green, grey</td>
<td>1.1 (0.6-2.3)</td>
</tr>
<tr>
<td>Blue</td>
<td>1.4 (0.8-2.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severe sunburn during lifetime</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>0.9 (0.6-1.3)</td>
</tr>
<tr>
<td>Study</td>
<td>Case-control:</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Walther et al, 2004, Ulm and Dresden, Germany, 1985-1997</td>
<td>213 cases with histologically confirmed BCC identified through dermatology departments, 411 dermatology and non-cancer patients from same departments</td>
</tr>
<tr>
<td>Rosso et al, 1996, 8 centres on France, Italy and Spain, 1989-1993, HELIOS study</td>
<td>1549 cases with histologically confirmed BCC cases diagnosed in 5 cancer registries and 2 hospitals, 1795 controls from 5 population registers and non-cancer, non-dermatology patients of 3 hospitals</td>
</tr>
<tr>
<td>Rosso et al, 1998, Europe, 1984-1993</td>
<td>420 cases with histologically confirmed BCC selected from HELIOS study, 835 controls selected from HELIOS study and population</td>
</tr>
<tr>
<td>Corona et al, 2001, Rome, Italy, 1995-1997</td>
<td>166 cases with incident BCC histologically confirmed diagnosed at referral hospital, 158 dermatology patients from same hospital</td>
</tr>
</tbody>
</table>

*Sunburn and sun exposure measure are italicised*
Appendix 4

Solar elastosis scoring sheet
<table>
<thead>
<tr>
<th>Study ID / Lesion Number</th>
<th>Amount of elastotic material adjacent to malignant tissue</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 = nil</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+ = minimal/mild</td>
<td></td>
</tr>
<tr>
<td></td>
<td>++ = moderate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+++ = severe</td>
<td></td>
</tr>
</tbody>
</table>